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Auditory ERP differences across a continuum of psychotic symptoms in non-clinical population

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Auditory ERP Differences Across a Continuum of Psychotic Symptoms in Non-

Clinical Population

By

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THESIS

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ABSTRACT

Psychosis is a term given to a mental state described as a loss of contact with the real world. The aim of this thesis was to examine early non-specific psychotic experiences in a healthy population by means of two self-report screening tools: Prime Screen and Youth Psychosis At-Risk Questionnaire-Brief, and place individuals on a psychosis continuum. Across this psychosis continuum, three event related potential (ERP) components were assessed: P300, Mismatch Negativity and N100. There is evidence that P300 and mismatch negativity amplitudes diminish in individuals with psychosis. Similarly, impaired N100 amplitude suppression (increased N100 amplitudes) during vocalization has been observed in psychosis. In the first experiment, participants vocalized a series of 'ah' sounds that were recorded and later played back in a talk-listen paradigm. We proposed that N100 amplitudes while talking would be reduced as compared to listening. However, as risk of psychosis increases, we predicted a failure of this N100 suppression (higher N100 amplitudes in individuals with higher risk of psychosis) during talking. In the second experiment, participants completed an oddball task in which a series of standard tones were presented. Duration deviant tones elicited P300 and mismatch negativity ERPs. We predicted that P300 and mismatch negativity amplitudes would decrease with increasing risk for psychosis. Furthermore, by using data from both experiments, a combination of ERPs was used to assess how well they were predictive of risk. We concluded that although risk was not associated with any ERP component in our population, results were fairly consistent with the general pattern

observed in previous literature among individuals at high risk for psychosis. The

combination of both the oddball and talk-listen paradigms provided better risk

predictability than either paradigm alone. These findings contribute to the development of

a risk predictability model that should allow efficient assessment of psychosis risk and

may improve the prognosis for people with psychotic disorders.

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ERP DIFFERENCES ACROSS A PSYCHOSIS CONTINUUM

<u>INTRODUCTION</u>

Mental health enables people to cope with their daily stresses and enjoy life. Absence of mental health, however, affects coping skills and makes managing life's problems more difficult, and may eventually take the form of mental illness. Psychosis is a term given to a mental state described as a loss of contact with the real world (Yung & McGorry, 1996). Psychosis is not a disease or a disorder itself, but rather a symptom that manifests in many disorders. Major psychotic disorders include schizophrenia, schizoaffective disorder and delusional disorder (American Psychiatric Association, 2013). Other disorders such as bipolar disorder, major depressive disorder, certain personality disorders and even substance abuse may exhibit clinical features of psychosis. Like any illness, psychosis commences with a series of non-specific symptoms that provide poor prognostic accuracy during the initial pre-clinical period i.e. the prodromal period (Yung & McGorry, 1996), but eventually develops characteristic diagnostic positive and negative symptoms. The DSM-5 criterion for schizophrenia lists five key symptoms: hallucinations, delusions, disorganized speech, disorganized behavior and negative symptoms (i.e. anhedonia or affective flattening). Presence of any two for a significant amount of time in a one-month period, in addition to continuous signs of disturbance persisting for a period of at least six months constitutes as diagnostic for schizophrenia. Disorganized speech may reflect disorganized thinking as seen in thought disorders, for instance blocking of thoughts or alogia. In addition to the five characteristic symptoms, there is significant social and occupational dysfunction. This thesis attempts

to examine these early non-specific psychotic experiences in a healthy population by means of screening tools that identify risk for psychosis. Using electroencephalographic correlates across participants, we tried to find association of risk for psychosis with each individual's brain responses using two paradigms, which are discussed in depth later. Furthermore, combination of data from both paradigms was used to assess how well they predict risk for psychosis.

Psychosis Prodrome

In medicine, a prodrome refers to a range of clinical features that appear before the manifestation of the characteristic diagnostic symptoms of a particular disease (Yung & McGorry, 1996). These features are subtle and nonspecific, for example in the case of measles. Fever and lethargy might appear during the prodrome, but these physical states are not specifically diagnostic until the characteristic rash appears (The Centers for Disease Control and Prevention, 2016). Similarly, a person may start showing signs of memory loss and behavioural impairments long before he/she actually fulfills the diagnostic criteria for Alzheimer's disease clinically (The Centers for Disease Control and Prevention, 2016). Likewise, a psychotic prodrome is a period of pre-psychosis in which the individual experiences a series of symptoms that deviate from typical behavior (Niendam et al., 2009). This prodromal period may commence with subtle negative symptoms that range from social withdrawal, lack of motivation, blunted affect and loss of interest in usually enjoyable activities (Niendam et al., 2009; Keshavan et al., 2011). These negative symptoms can be hard to identify, however, as the disorder eventually progresses, it manifests characteristic positive symptoms such as hallucinations,

delusions and disorganized speech (DSM 5; International Statistical Classification of Diseases and Related Health Problems, 10th Revision; Keshavan et al., 2011) that can severely impact a person's quality of life. Therefore, clinicians seek early diagnosis and prompt proactive treatments for psychotic disorders.

Psychosis Proneness-Persistence-Impairment Model

Epidemiological research has shown that non-specific psychotic experiences are far more prevalent (8% of the population) than clinically evident psychotic disorders (Os et al., 2009). A continuum of psychosis exists in the general population (Os et al., 2009; Os, 2003), varying in levels of schizotypy. It ranges from typical healthy behaviour to non-clinical psychotic experiences, which with persistence of symptoms eventually lead to full-blown psychosis with characteristic symptoms, such as delusions and hallucinations (Figure 1). The psychosis proneness-persistence-impairment model (Os et al., 2009) describes this transition from subclinical psychotic incidences to psychotic episodes that ultimately require medical attention. In this model, early psychosis vulnerability is transitory but increases psychotic proneness. Upon recurrent environmental stress (e.g. discrimination, major life event, unemployment etc.), there is prolongation and worsening of proneness, leading to persistence of psychotic incidences. Persistence of psychotic incidences eventually leads to serious psychotic symptoms.
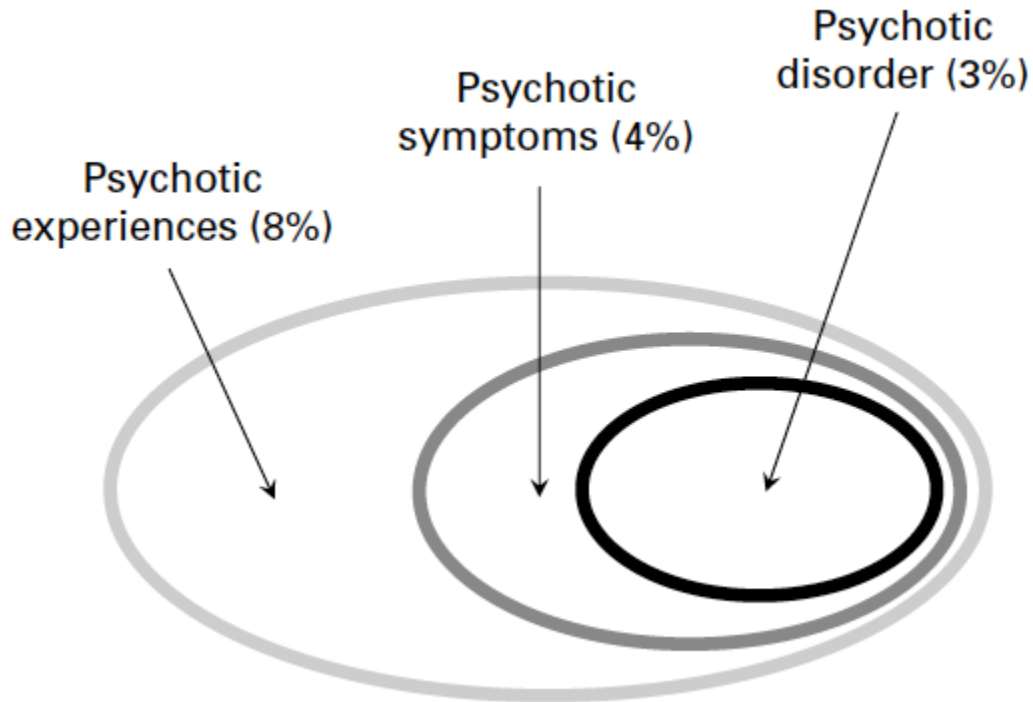
Figure 1. Psychosis: variation along a continuum (adapted from Os et al., 2009).

Previous research has tried to develop a marker for early diagnosis of psychosis in the prodromal phase before its progression into a full-blown psychotic episode (Bruggemann et al., 2013). A cohort study showed that a clinically evident psychotic disorder could be traced back to subclinical non-specific symptomatology of psychosis apparent up to 8 years prior to diagnosis (Dominguez et al., 2011). The Zurich 20-year longitudinal study (Rössler et al., 2007) further highlighted this point by assessing a sample of 591 participants from the general population aged 20-21 years old and followed up at ages 23, 28, 30, 35 and 41 years. It concluded that the pathways to psychotic disorder could be studied well before the disorder manifests clinically. This study also supported the existence of a continuity of psychotic symptoms alongside normal behaviour, which

further reinforces how essential it is to recognize the non-specific symptoms of psychosis.

A key reason to focus on individuals in their prodromal period while developing a marker for early diagnosis is to exclude the influence of drug treatment. Because a lot of literature has focused on schizophrenia and bipolar disorder patients undergoing treatment, it is not easy to factor out the effect of drug treatment (Murphy et al., 2013) and relate any differences between healthy populations and these clinical populations directly to the severity of disease pathology. For example, it is known that antipsychotic medications may distort neural responses to stimuli (Neuhaus et al., 2013; Todd et al., 2012). As well, first generation antipsychotics (e.g. haloperidol) or typical antipsychotics may be associated with significant reduction in volume of the frontal area, temporal-insular areas and the precuneus (Dazzan et al., 2005), while at the same time may cause enlargement in the basal ganglia (Vita et al., 2012). On the contrary, second generation antipsychotic medication (e.g. olanzapine) may have neuroprotective effects in patients with psychosis. That is, they appear to counter-act, at least partially, the cortical gray matter loss that is typically evident in psychosis (Vita et al., 2012). Atypical antipsychotic drugs are also associated with enlargement of the thalami (Dazzan et al., 2005). For these reasons, it is essential that a study is conducted on individuals from a non-clinical community sample that may be in the prodromal stage, so as to eliminate the effect of drugs, and neural markers are identified across a continuum of psychotic symptoms.

EEG correlates in psychosis

A vast number of electroencephalogram (EEG) studies have been conducted to identify markers for psychosis (Baldeweg et al., 2004; Ford et al., 2001; Neuhaus et al., 2013). EEG detects electrical activity in the brain. Event-related potentials (ERPs) are scalp recorded voltage changes observed on EEG that reflect neural activity related to internal cognitive events. These events occur in response to outside stimuli, resulting in a series of positive and negative peaks (Luck et al., 2011). A number of ERP abnormalities have been observed in patients with psychosis that may serve as diagnostic markers (Oestreich et al., 2015b; Hsieh et al., 2012; Simons et al., 2011; Neuhaus et al., 2013). Three ERP components focused on as part of this thesis are the P300, the Mismatch Negativity and the N100.

P300

Since 1965, when the P300 ERP component was first discovered (Sutton et al., 1965), the P300 has been considered a promising component to assess cognitive impairment (Ford, 1999). Recent literature provides support for the P300 as a marker for psychosis (Neuhaus et al., 2013). The P300 is a positive deflection between 250 ms and 500 ms post stimulus, with maximum amplitude at the central electrodes of the 10-20 system (Towle et al., 1993), namely Fz, Cz and Pz (Polich, 2007; Duncan et al., 2009). Amplitude is the difference between the baseline pre-stimulus voltage and the maximum ERP voltage in a specific time interval, in this case between 250 ms and 500 ms (Polich, 2007). When there is no change in a series of similar stimuli, a memory template or a 'schema' is maintained, as the brain perceives the sensation of that stimulus, for example the sound of a tone, in case of auditory paradigm. If a new stimulus is presented, the P300

is hypothesized to reflect attentional processes that update the schema (Polich, 2007).

The P300 is usually elicited in a traditional two-stimulus oddball paradigm (Polich et al.,

2007). A series of standard stimuli are presented that elicit sensory ERPs. A new stimulus

in the form of an infrequent deviant stimulus is presented between a series of the more

frequent standard stimuli. This new stimulus generates a P300 ERP. The deviance can be

across a range of different dimensions such as frequency, duration, intensity and location

(e.g. Atkinson et al., 2012; Duncan et al., 2009; Nagai et al., 2013).

P300 and psychosis. Attention can either be engaged automatically or effortfully

(Ford et al., 1996). However, separate experimental paradigms are employed to elicit an

automatic P300 (P3a) or an effortful P300 (P3b). Also, different brain regions elicit

respective P3a and P3b as different neural processes are thought to be involved in

paradigms that require either automatic and effortful responses to deviant stimuli (Ford,

1999). The P3a or automatic P300 is elicited by an infrequent stimulus, in which no

conscious effort by the participant is required to identify the oddball. P3a may be elicited

by startling events or novel sounds (noise burst or dog barking) in case of auditory

stimuli. The source of the P3a has been localized to the frontal cortical region (Ford,

1999). By contrast, the P3b or effortful P300 is elicited during an oddball experiment in

which the participant is required to respond to the deviant stimulus. For example, the P3b

may be elicited by target detection tasks that require a button press response. The P3b has

been localized to the temporo-parietal cortical structures (Ford, 1999). In healthy

individuals, P300 amplitudes increase with increased attentional demand. Attentional

deficits are a common symptom of schizophrenia (Ford, 1999; Shen et al., 2014) and may

contribute to an inability to recognize the rare stimulus in oddball paradigms, as reflected by the reduced P300 amplitudes observed in this population during oddball tasks.

Attenuation of P300 amplitudes is found in patients with schizophrenia as compared to controls, during passive auditory oddball paradigms and also those requiring a button press response (Simons et al., 2011; Bramon et al., 2004). Reduced auditory P300 amplitude has also been considered a vulnerability or a trait marker for psychosis (Stelt & Belger, 2007). Moreover, P3a amplitude reduction in a passive oddball experiment has been observed in individuals who are at high risk of developing psychotic illness (Atkinson et al., 2012). However, P300 amplitudes have not been observed to decline with disease progression (Devrim_Üçok et al., 2016). Devrim-Üçok and colleagues (2016) tested patients with first episode psychosis and then again after six years. No progressive decline in the P3b was observed as the disease progressed. In other words, P300 amplitudes are already at their smallest at the time of the first episode of psychosis. This reaffirms the need for a study of the prodromal period before the onset of characteristic features of psychosis itself, because reductions in P300 amplitudes occur before any distinctive disease symptom manifests.

It should also be noted that diminished P300 amplitudes are not only explained by the diagnosis of a psychotic disorder, but also by gray matter deficits in frontal and temporal brain regions (Ford et al., 1994). There is an assumption that reduced gray matter volumes are related to smaller P300 ERPs (McCarley et al., 2002). Defective automatic attention (P3a) predicts decreases in gray matter volume that may occur as a result of psychosis. On the other hand, impaired effortful attention (P3b) predicts presence of schizophrenia itself (Ford et al., 1994). Although MRI studies suggest that there is

accelerated gray matter volume reduction in schizophrenia (Vita et al., 2012), a recent
longitudinal study found an age-related progressive decline in P300 amplitudes in healthy
population (Devrim_Üçok et al., 2016) as well. However, this age-related decline occurs
after adolescence (Dinteren et al., 2014). On the contrary, the P300 amplitudes in
psychosis are already at their smallest at the time of first episode of psychosis, as
discussed earlier. The psychosis related gray matter volume changes in different brain
regions are present before the onset of psychosis, i.e. during the prodromal phase, and
progress over time during transition to psychosis (Vita et al., 2012; Wood et al., 2008).
Since we know that the typical age of onset of first psychotic episode is around 23.7
years (Rajji et al., 2009), this is one of the reasons why testing P300 amplitudes in
adolescence and early adulthood can be a reliable marker for psychosis that can predict
onset of any psychotic disorder.

   P300 latency. Auditory P300 latencies have been observed to be longer in persons
suffering from psychosis than in healthy individuals (Stelt & Belger, 2007). For healthy
individuals, P300 latencies are longer when the deviant stimulus is difficult to
discriminate and it takes longer to identify the target stimulus (Linden, 2005). However,
more prolonged P300 latencies have been observed in first episode schizophrenia patients
when there is a small difference between the standard and the infrequent oddball stimuli
(Qiu et al., 2014). A meta-analysis by Qiu and colleagues (2014) concluded that since
individuals with psychosis typically have attentional deficits, it seems logical that their
latencies would be longer than that of healthy controls as individuals with psychosis
would find it harder to differentiate the deviant stimulus among a string of standards.

In short, the P300 ERP is elicited in response to an unexpected rare stimulus. All forms of P300 in response to an oddball have shown reduced amplitudes in individuals with psychosis. Diminished P300 is not only evident in psychosis but is also predictive of gray matter volume deficits. In psychosis however, most of the P300 amplitude reduction is seen during the prodrome period, suggesting that this ERP component may be a good predictor of psychosis. Since our focus is only on P3a, the term P300 has been used interchangeably for P3a throughout the rest of this document.

Mismatch Negativity (MMN)

The MMN ERP component is elicited by the detection of a deviant event (Kargel et al., 2014). Similar to the generation of P300, MMN is associated with a change in the pre-existing 'schema' of similar events. Thus, it is a context-dependent response, observed 100-250 ms from the onset of the deviant event (Todd et al., 2012; Bendixen et al., 2012; Bruggemann et al., 2013; Garrido et al., 2009) and exhibits strongest amplitudes at Fz and Cz electrodes (Duncan et al., 2009). MMN is calculated as a difference wave between ERPs in response to standard stimuli and infrequent deviant stimuli (Nagai et al., 2013a). It represents pre-attentive sensory memory (Nagai et al., 2013b). It may be generated across a range of different dimensions of deviance, such as frequency, duration, intensity, location (Naatanen et al., 2004), inter-stimulus interval (Näätänen et al., 2004; Murphy et al., 2013) or violations in phoneme regularity (Naatanen et al., 1997).

MMN waveform generation. There are two well-established hypotheses regarding the source of MMN waveform generation. The first hypothesis is the 'model adjustment

hypothesis' (Winkler et al., 1996). This hypothesis is supported by the fact that a pre-existing schema is formed in response to a series of regular external stimuli. These stimuli form a memory trace, which in the auditory domain is termed as echoic memory (Garrido et al., 2009). In healthy individuals the duration of echoic memory is at least 10 seconds (Böttcher-Gandor and Ullperger, 1992). This memory trace is used as a template by the brain against which future incoming stimuli are compared. When there is a violation in this regularity, the brain automatically updates the schema and the MMN waveform results from this mismatch. Larger MMN amplitudes are observed with rarer events or when there is a larger difference between the standard and deviant stimuli (Todd et al., 2012). In the model adjustment hypothesis, two underlying mechanisms are proposed to be involved (Garrido et al., 2009). The first process is a sensory memory mechanism that reflects sensory processing of the physical properties of the stimulus, for example a tone as in the case of auditory paradigms. The sensory memory mechanism is reflected by activity in the temporal area (auditory cortex) in fMRI-EEG studies peaking between 90 ms and 120 ms (Opitz et al., 2002). The second process is an attention switching process that accounts for the change in the regular pattern of incoming stimuli. This redirection of attention to the deviant stimulus is reflected by activity in the prefrontal region, observed in the time range of 140-170 ms (Opitz et al., 2002). An fMRI-EEG study (Doeller et al., 2003) using pitch deviant auditory stimuli showed double peaks that correspond to these two separate time windows as evidence of the underlying processes of MMN generation in fronto-temporal brain regions.

The second hypothesis for explaining MMN generation is the 'adaptation hypothesis' (May et al., 1999; Jaaskelainen et al., 2004). According to this hypothesis, each stimulus

generates an N100 ERP component, elicited as a negative deflection at 100 ms post stimulus. This N100 is associated with early stimulus processing. The similarity of stimuli in oddball paradigms causes adaptation that in turn reduces the N100 response. The N100 waveform diminishes as adaptation occurs in response to regularity. Subsequently, in response to a deviant stimulus, the N100 response is larger. As a result, the MMN would appear as a difference wave of N100s of standard from deviant respectively. Critiques to this hypothesis argue that adaptation alone can't explain MMN generation as MMN duration and latency does not match that of the N100 (Winkler et al., 1997; Naatanen et al., 2005). Similarly, MMN has been observed in comatose patients (Duncan et al., 2009), where there is an absence of N100s in response to stimuli.

A review by Garrido et al. (2009) suggested a unified approach using the model adjustment and the adaptation hypotheses to explain the underlying mechanism for MMN generation. 'Predictive coding' combines the two in a way that integrates the external stimuli and the pre-existing schema in the brain in a hierarchical fashion. The higher cortical areas store information of previously acquired information whereas, the lower cortical areas rely on the sensory input of incoming stimuli. As a result, the higher areas try to fit the incoming new events to their learned representations while the lower areas attempt to balance the predictions with the actual input. Sensory inputs reduce the prediction error through regular interactions in the various cortical levels. In other words, MMN generation is not just driven by the occurrence of deviant stimuli. Instead, a pre existing schema is maintained against which the brain makes inferences in a top-down as well as a bottom-up approach. Hence, MMN is elicited when the higher cortical areas are unable to predict the sensory input. In simpler terms, predictive coding combines the

model adjustment and the adaptation hypotheses as it maintains a schema and changes the schema based on lower level input from the sensory cortices.

MMN and psychosis. MMN amplitudes are reduced in patients with psychosis. Previous research has found that MMN reduction has a positive predictive value of 92% for schizophrenia (Bodatsch et al., 2011). However, diminished MMN amplitudes may not be specific to any particular disease (e.g. schizophrenia) but to deficits of cognitive function, that are common to most psychoses (Kargel et al., 2014) and also age related cognitive declines, for instance as seen in age related Alzheimer's disease (Duncan et al., 2009). In a meta-analysis by Umbricht and Krljes (2005), the effect size of MMN in response to deviations in duration was found to be 40% larger than that for MMN in response to deviations in frequency in patients with schizophrenia. This suggests that duration deviant MMN waveforms are more affected by psychosis as compared to frequency deviant MMN. Furthermore, there is evidence that the reductions in MMN amplitudes in response to frequency deviance develop over the course of the psychotic illness (Murphy et al., 2013; Kargel et al., 2014). Conversely, duration (Nagai et al., 2013a; Murphy et al., 2013) and intensity deviant (Kargel et al., 2014) stimuli show MMN impairment before the onset of psychosis. Consequently, since MMN in response to duration deviants seem to be the most affected in the prodromal period, we concentrated on duration deviance for this study, as our targeted population does not have clinically evident disease. Previously, significant reduction in the MMN amplitudes for duration deviants has been observed across people with schizophrenia (Baldeweg et al., 2004; Kargel et al., 2014), first episode psychosis patients (Hsieh et al., 2012), ultra-high at risk for psychosis groups (Atkinson et al., 2012), early-broad at risk (marginal risk for

psychosis) groups (Hsieh et al., 2012), children with antecedents (social, emotional or

behavioural symptoms) of schizophrenia (Bruggemann et al., 2013), as well as first

degree relatives of patients with psychosis (Michie et al., 2002), as compared to healthy

individuals.

A number of hypotheses have been used to explain why the MMN waveforms are

affected by psychosis. As explained earlier, frequently encountered repetitive stimuli

form a memory trace (Todd et al., 2012). In response to a deviant stimulus, there is a

violation of the memory-based expectation and a MMN waveform is generated. It is

proposed that the individuals with psychosis are unable to recognize the difference

between a deviant stimulus in an oddball paradigm and the preceding regular (standard)

stimuli (Todd et al., 2012). However, some have argued against this proposition by

stating that there is an imprecision in the perception of the error size in psychosis. Since

larger MMN amplitudes are observed with increasing deviance size, even in psychosis,

then there may instead be impairment in the quantification of the size of the difference

between the standard and the deviant stimuli that reduces MMN amplitude (Todd et al.,

2012). Therefore, it may actually be a dysfunction in the perception of error size that

reduces MMN amplitudes (Todd et al., 2012). The cortex is unable to detect the degree of

change in the newer events as compared to previous representations. This reduced range

of variation detection by the cortex leads to a notion that perhaps, in psychosis, MMN

amplitudes plateaus earlier as compared to that of healthy individuals. Consequently,

there is a smaller upper limit to MMN amplitude leading to a reduced dynamic range

(Todd et al., 2012; Todd et al., 2013). In other words, if we say that a 5 µV MMN

amplitude is necessary for functional integrity, for instance, then a smaller upper limit of

MMN amplitude may be 2 µV. Accordingly, if an absolute threshold of MMN amplitude is important for functional integrity, then there is inadequate cortical activation in response to a newer/unexpected event (Todd et al., 2012). Lack of motivation and passiveness in psychosis may stem from this inadequate activation in response to new events (Javitt et al., 1995). As a result, individuals with psychosis do not possess the same drive for environmental exploration and show a lack of interest in usually pleasurable activities (Javitt et al., 1995). However, if a certain threshold MMN amplitude is not necessary and any relative amplitude for MMN shows functional relevance, the brain will be easily and more frequently be activated by new events in individuals with psychosis (Todd et al., 2012). As a result, these individuals may have difficulty in concentrating on a single task and get distracted easily by their surroundings. In other words, there may be a certain degree of hyper vigilance, as the brain perceives events that are inaccurately amplified. Also, this amplified attention to irrelevant cues may underlie a patient's proneness to hallucinations (Yoon et al., 2015; Whitford et al., 2012). Either way, MMN is considered a strong candidate for being a marker to identify pre-psychosis (Hsieh et al., 2012; Nagai et al., 2013a), because psychosis-prone individuals do not have the same level of cortical activation in response to unexpected events as healthy controls.

A recent study investigated MMN in persons ranking high on schizotypy (Broyd et al., 2016). Despite the substantial evidence on MMN amplitude reduction in at-risk population, there was no significant MMN attenuation in schizotypal individuals. One of the explanations given by Broyd and colleagues (2016) was that perhaps the MMN is more related to the disease state and not schizotypy scores across a continuum of

psychosis. Since it was a small sample size, it could be possible that although they ranked higher on schizotypy, their participants were non-converters to psychosis. In other words, MMN could be a marker of conversion to psychosis and not just indicative of scoring high on a schizotypy questionnaire. Regardless, this explanation could be strengthened with replication of the study including more neurophysiological markers for analysis, further signifying a need for the present study.

MMN latency. MMN latency is the time from the onset of the stimulus until the maximum peak of the MMN waveform. In other words, it is the time by which the deviant stimulus from a series of regular stimuli is recognized as being different resulting in a MMN peak (Kargel et al., 2014). MMN has a latency window of 100-200 ms (Lindin et al., 2013). Unlike the evidence for MMN amplitude, there are inconsistent findings regarding whether there are differences in MMN latencies between the population with psychosis and healthy controls. While some authors have reported shorter MMN latencies in people with psychosis (Kargel et al., 2014), a few have found no significant differences (Murphy et al., 2013) among the at risk population and healthy controls. Based on the hypotheses for MMN waveform generation, a shortened latency may indicate dysfunction in early stimulus processing that may introduce errors and lead to inaccuracy in integrating new information into existing neural networks (Kargel et al., 2014). This, in turn may lead to the cognitive impairment seen in schizophrenia.

N100

The N100 ERP component is also affected by psychosis (Ford et al., 2013). The N100 is a negative deflection that occurs 80 to 120 ms after the onset of an auditory stimulus, with maximal amplitude at Fz, FCz and Cz scalp distribution (Ford et al., 2010). It

reflects auditory processing in the cortex in response to a stimulus. Information

processing is done by a feedforward mechanism (Heinks-Maldonado et al., 2007).

Specifically, whenever an action is carried out, a copy of the motor command known as

the efference copy is sent to the cortex. A predicted sensory feedback resulting from that

action, known as the corollary discharge is generated. The corollary discharge is then

matched with the actual sensation and a sensory reafference is generated i.e. the net

difference in sensation. This efference copy / corollary discharge mechanism offer a self-

monitoring system that can compare predicted and actual feedback and dampen the

sensation of the action. The suppression of the sensory effect marks that particular action

as originating from self. This is supported by the fact that as a person talks frontal cortical

activity increases with a simultaneous decrease in activity in the temporal region

(Oestreich et al., 2015a). It is hypothesized that this suppression is brain's way of

distinguishing between self and the outside world. The closer the match is between the

predicted and the actual sensation, the greater is the N100 suppression (Ford et al., 2013).

In the auditory system, the motor command to talk is accompanied by an efference copy.

The corollary discharge is generated for the intended sound that will be heard. When the

actual sound heard is the same as that intended by the corollary discharge, there is

suppression of activity in the auditory cortex.

N100 and psychosis. Failure to distinguish between self and the external surroundings

is the hallmark of hallucinations, a characteristic symptom of psychosis. Ford et al.

(2013) assessed auditory N100 suppression during talking among people with

schizophrenia, schizoaffective disorder and bipolar disorder and compared them with

healthy controls. Significantly reduced N100 suppressions (increased N100 amplitude)

were observed while talking when participants were instructed to vocalize and later listen

to their own recordings (Ford et al., 2001; Ford et al., 2010). This suggested that the

corollary discharge mechanism might be disrupted in such individuals. There is imprecise

dampening of the sensation of the action. In other words, the sensory input of the self-

generated vocalizations is not suppressed. Consequently, individuals with schizophrenia

form imprecise corollary discharges and lack the ability to predict a vocalization that is a

result of their own speech. Furthermore, persons ranking high on schizotypy (high risk

for psychosis) also showed significant N100 suppression failure (Oestreich et al., 2015).

It may in fact be the disruption of this mechanism that underlies psychotic symptoms,

such as hallucinations (Ford et al., 2013).

<u>Neurophysiologic basis of psychosis</u>

At a neurochemical level, hyper-responsiveness of the dopamine system has been

considered to be the main cause of psychosis and is associated with its positive symptoms

(Howes et al., 2012). Evidence for this comes from the fact that the primary mode of

action of anti-psychotic drugs used today is blocking the D2 receptors (Grace, 2016). D2

receptors are a type of dopamine receptors that are present on cell membrane surfaces and

allow interaction with the neurotransmitter dopamine. Furthermore, dopamine-releasing

agents such as amphetamine cause paranoid psychosis (Harrison, 1999). The

dopaminergic over-activity can be due to high levels of dopamine itself or as a result of

increased sensitivity, as in case of increased numbers of dopamine receptors (Harrison,

1999).

At a neuronal level, myelination of axons of the frontal and temporal lobes is

considered deficient in individuals with psychosis (Whitford et al., 2012). Glial cells or the non-neuronal cells provide support to the neurons of the central and the peripheral nervous systems. One such type of glial cells is oligodendrocyte that provides support to the axons of the central nervous system by forming a myelin sheath around the axons (Simons & Nave, 2015). Myelination of axons increases the speed of conduction of the neuronal impulse. These myelinated axons are often bundled together to form white matter fasciculi. It is suggested that there are abnormalities in the white matter fasciculi that may consequently cause conduction delays (Whitford et al., 2012). According to a study, it is further suggested that structural abnormalities in the fasciculi connecting the frontal and the temporal lobes may cause delay in generation of corollary discharge signals (Whitford et al., 2012). As a result, corollary discharge signals occur too late to suppress the sensory activation so as to tag the source as self. This causes confusion in regards to the source of the action and underlies hallucinations. One noteworthy point here is that the frontal fasciculi are the last to structurally develop, with myelination of the axons continuing well into adolescence and adulthood (Tamnes et al., 2010). This is the critical time for the age of onset of prodromal symptoms (Rajji et al., 2009). This suggests that frontal fasciculi maturation would be impacted by occurrence of prodromal symptoms in an adolescent already prone to psychosis and faces frequent environmental stresses as proposed by the psychosis-proneness-persistence-impairment model, mentioned earlier (Os et al., 2009).

Disorganization of the fronto-temporal functional connectivity has been observed to be at the core of the pathology of schizophrenia (Gaebler et al., 2015) and is evident in fMRI studies conducted on individuals in the prodromal period. There is hypo-

connectivity between bilateral Heschl's gyrus and the dorsal anterior cingulate cortex

during a resting state (Yoon et al., 2015). Conversely, hyper-connectivity is seen between

the left planum temporale and bilateral dorsolateral prefrontal cortex. A positive

correlation between this hyper-connectivity and psychotic symptoms of delusions and

hallucinations has been observed. The insula and the anterior cingulate cortex encompass

the salience network (Seeley et al., 2007). Hypo-connectivity has been observed between

the salience network and the auditory cortex in ultra-high risk for psychosis individuals,

who also show reduced MMN amplitudes (Yoon et al., 2015).

<u>Hypothesis</u>

As discussed, a lot of research has been conducted to identify EEG abnormalities in

psychosis. Still, it remains to be determined whether these are vulnerability markers or

mere ERP correlates. In this study, the objective is to use a combination of known

abnormal ERP components in patients with psychosis to identify a marker that could

serve as an endophenotype for early diagnosis in a non-clinical population. Our

hypothesis is that a continuum of psychosis exists across any given population that is

measurable by screening tools and ERP alterations. We also hypothesize that these

variations in ERP components are directly proportional to risk for psychosis. In other

words, we propose that there will be positive correlation between the questionnaire scores

and the ERPs. Our ultimate aim is to be able to identify vulnerable individuals before

clinically evident symptoms appear so as to better predict the first episode of psychosis

and enable a proactive treatment approach.

There is a large literature on P300 and MMN elicited using oddball paradigm and N100 elicited using the talk-listen paradigms. Our secondary aim was to assess these components on the same population to remove any sampling bias, and also to be able to assess which of the three ERP components is the most ideal to identify an early prodrome stage and has the most predictive value.

Experiment

Participants were recruited from the undergraduate level at Wilfrid Laurier University. Participants reported no previous diagnoses of any psychotic disorder or any history of taking psychoactive medications. The objective was to obtain data from a population that has clinically normal behavior. The typical age at onset of first episode psychosis is observed to be on average 23.7 years (Rajji et al., 2009). Hence, the time before that age is critical for observing any behavioral changes that occur before a person goes on to develop psychosis later in life. Since the P3a and MMN amplitudes have also been observed to decline with age (Nowak et al., 2016), with the average age of decline starting from mid-30s (Todd et al., 2012), the goal was to recruit participants between 18-28 years of age. Participants were selected by preliminary screening. A variety of clinician rated and self-report questionnaires for identification of individuals across this continuum have been created (Daneault et al., 2013). The set of tools that tap prodromal symptoms can be divided into two approaches, based on their respective approach. The first approach is the basic symptoms approach that identifies early prodromal phase (Daneault et al., 2013). It detects early subtle changes in perception and cognition. The second approach is the attenuated positive symptom approach that identifies features of

the late prodromal period (Daneault et al., 2013). Inspired by these questionnaires, a set

of screening tools has been formulated to identify atypical behavior to diagnose psychosis

early. The Youth Psychosis At Risk Questionnaire-brief (YPARQ-B) (Kline et al., 2012;

Addington et al., 2015) is a 28 item self-report questionnaire, developed from the

Comprehensive Assessment of At-Risk Mental States, an instrument based on the

attenuated positive symptoms approach (Olsen & Rosenbaum, 2005). It has an overall

accuracy of 71% (Kline et al., 2012) and has the highest positive predictive value and

specificity among other screening tools for the attenuated positive symptoms approach

(Kline et al., 2012). In addition to the YPARQ-B, participants were administered the

Prime Screen (Kline & Schiffman, 2014; Kline et al., 2012). The Prime Screen is

developed from Structured Interview for Psychosis Risk Syndromes. It is based on the

attenuated positive symptoms approach and contains 12 Likert-type items. It has a

sensitivity of 0.90, suggesting that Prime Screen has a 90% chance of correctly selecting

true positives (Kline et al., 2012). We selected individuals across a continuum of scores

obtained using these two screening tools. The range of scores of the questionnaires, we

hypothesized, depicted a continuum of psychotic symptoms based on the levels of

schizotypy.

In this study, we executed two separate paradigms. The first paradigm was the Talk-

Listen paradigm (Ford et al., 2010), which was used to determine the level of N100

suppression across the continuum of symptoms. For the second paradigm, participants

completed a passive auditory oddball task to identify differences in the P300 and MMN

components across the continuum of symptoms. As previously mentioned, oddball

experiments may have multiple dimensions of deviance among auditory stimuli that are

used. We used duration deviant two-tone auditory stimuli for the oddball paradigm. Also, duration increment deviants, which are deviant stimuli that are longer in duration as compared to standard stimuli, were used in contrast to duration decrement deviants, that involve deviant stimuli that are shorter in duration as compared to standard stimuli. Previous evidence suggests that duration increment MMN amplitudes are significantly reduced in the at-risk population in comparison to duration decrement that may not be significantly affected (Todd et al., 2013). We used a pure tone of 60 ms as a standard stimulus. As a duration deviant stimulus, a pure tone of 100ms was used in the first half of the oddball experiment and a 150 ms tone was used in the second half of the experiment. Previously, significant effects have been observed in healthy individuals when using different magnitudes of deviant stimuli in an oddball task (Naˑäˑtaˑnen, 2008; Pakarinen et al., 2007). However, to the best of our knowledge there are no data regarding effects of using multiple magnitudes of the same dimension of deviance regarding the at-risk population. Since there is a dysfunction of prediction of error size involved in the predictive coding hypothesis in people with psychosis, our hypothesis was that increasing the error size, by means of using a separate magnitude of duration deviance in the oddball experiment, would demonstrate a significant difference in MMN amplitude reduction. This means that as the difference between the standard and deviant stimulus would increase, the MMN amplitudes would increase as well.

In addition to the P300, MMN and N100, we identified any significant differences in the general waveform.

METHODS

Participants

Participant recruitment and data acquisition were completed at the Wilfrid Laurier University after approval from the university's Research Ethics Board. Fifty-eight Psychology undergraduate students (mean age = 19.2, SD=2.0; 37 women) were recruited. All participants were right-handed. Participants reported normal hearing, normal or corrected to normal vision, no visual impairment that could not be improved with corrective lenses (e.g., cataract, glaucoma, etc.), no speech or language impairment, and no attention deficit disorder. No participant reported previous diagnosis of any psychiatric illness or taking any psychoactive medications. All students were compensated with course credit for their participation. Informed consent was obtained prior to testing.

Apparatus

Prior to commencing the experimental session, participants completed a language and handedness questionnaire. They were asked to complete the Prime Screen and Youth Psychosis At-Risk Questionnaire-Brief (YPARQ-B) questionnaires. On the basis of each individual's performance on the latter two questionnaires, participants were given a score that could range between 0 and 72 for Prime Screen and 0 and 28 for YPARQ-B.

A NeuroScan GSN 64 1.0 Ag/AgCl electrode Quik-cap (Compumedics, Charlotte, NC, USA) was used to record ERPs. Electrodes were positioned according to the International 10-20 EEG System with one ground electrode and linked mastoid electrodes

as reference. Surface electromyographic electrodes were positioned at the outer canthii of the eyes. Two more were positioned above and below the left eye for subsequent artifact removal during analysis. Each participant was fitted with Etymotic ER-3 insert headphones (Etymotic Research, Elk Grove Village, IL) and a headset microphone (Countryman Isomax E6 Omnidirectional Microphone). Testing was completed in a dimly illuminated electrically shielded booth (Raymond EMC, Ottawa, ON, Canada). They were seated on a comfortable chair with a 15-inch LCD monitor in front of them.

The presentation of stimuli was done controlled by programmable experiment generation software Stim2 (Compumedics, Charlotte, NC, USA). The electrical signals were acquired across all 64 channels and sent through the headbox to two Synamps 2/RT amplifiers (Compumedics, Charlotte, NC, USA). ERPs were then recorded using the NeuroScan Acquire software for off-line analysis. An 8-track voice recorder (Fostex MR-8HD Digital Multi Track Recorder, Tokyo, Japan) was connected for recording vocalizations and tones on separate channels. This recorder was further connected to another voice recorder (TASCAM HD-P2, Montebello, CA, USA) to allow for recording the tracks of the first recorder on a single track along with an initial trigger tone to mark initiation of the tracks, for playback in the latter part of the experiment.

Procedure

The electrode cap was placed onto the participant's head. Electrode Cz was visually centered above the central vertex found halfway between the glabella and the external occipital protuberance medially and the preauricular points laterally. Electro-gel was used to improve conduction between the skin and the electrode surface. Surface

electromyographic electrodes were positioned at the outer canthii of both eyes and above

and below the left eye. Mastoid electrodes were placed on the mastoid process behind

each ear for later referencing in Scan 4.5 (Compumedics, Charlotte, NC, USA).

ERPs were elicited using two paradigms: the Talk-Listen Paradigm and the

Oddball Paradigm. During the experiment, Stim2 presented a fixation cross on the screen.

Participants were instructed to fixate on the cross throughout the experiment except

during pre-assigned break intervals.

Talk-Listen Paradigm

Participants performed the Talk-Listen paradigm, adapted from Ford et al., 2010,

first. There were 2 phases for the Talk-Listen portion of the experiment: the Talk phase

and the Listen phase.

In the Talk phase, participants were instructed to vocalize short, sharp 'ah' sounds

every time the red fixation cross changed its color to green. The green fixation cross

appeared for 300 ms so that the participant would vocalize for ~300ms. Participants'

vocalizations were heard through earphones and sent to the first voice recorder, where

they were recorded. There were 150 vocalizations in all, divided into sets of 25 within 6

blocks, with pre-assigned 10s breaks in between each block. To mark the onset of the

green cross, a pure tone of 50ms from Stim2 was sent to Track 2 on the first recorder,

while simultaneously a TTL was sent to NeuroScan Synamps 2/RT amplifiers to mark

the green cross onset for later off-line analysis. The vocalizations were heard by

participants in real time. Before starting the experiment, participants did a practice run

with a few trials with the experimenter in the booth to make sure the 'ah' sound was

properly vocalized.

In the *Listen* phase, participants listened to their recorded voice from the Talk phase. For calculating voice onsets during the Listen phase for later analysis, a 1000 ms long tone was sent to the second recorder followed by the entire recording of the Talk phase.

Participants were instructed to speak with minimal jaw movement and to not blink or otherwise move during the trial, i.e. while vocalizing or listening to an 'ah' sound, so as to minimize motor artifacts. Participants could blink or move while the fixation cross was red or during the 10 s breaks.

Oddball Paradigm

After completing the Talk-Listen task, participants were exposed to the auditory oddball paradigm. This phase was divided into two parts on the basis of the duration of the deviant tone.

During the first part, participants listened to the repetition of a frequent non-target standard pure tone (500Hz) of 60 ms, 1020 times (85% of total trials). An odd, rare target stimulus of 100 ms was presented 180 times (15%) pseudorandomly. These 1200 trials were divided into 3 blocks of 400 trials each with 5 s intervals between them. The inter-stimulus interval was 500 ms and the total time for each block was ~ 4 minutes. Participants were instructed to ignore the tones and to only fixate on the cross. The events were marked in the NeuroScan Acquire software for further analysis.

In the second part, the standard tone was again 60 ms but the deviant tone was 150 ms long. The rest of the experimental details were the same as the first part.

Participants were encouraged to take a break in between the two halves of the oddball experiment, as it was boring. They were instructed to blink as few times as possible and to not move during the entirety of the oddball experiment.

ERPs were constantly monitored while the Talk-Listen and the Oddball experiments were running to ensure that there were no unusual artifacts, loose electrodes or unusual noise. At the end of the experiment, the participants were debriefed.

Analysis

Analysis was completed in three steps: voice, ERP and statistical analyses.

Voice Analysis (for Talk-Listen experiment only)

Audacity (Version 2.0.5, Boston, MA, USA) was used to ensure all triggers and corresponding vocalizations were present. Absent or extra vocalizations were noted in order to exclude those trials from the ERP analysis. Voice data (.wav files) were segmented into individual vocalizations using a custom MATLAB (MathWorks, Massachusetts, USA) script. A custom PRAAT (Version 5.3.40) script found the onset of each utterance and then the time difference between the onsets of the 1000 ms long tone that marked the start of the Listen phase and the first voice playback was calculated manually using Audacity. This offset time was added to the voice onset times found using PRAAT. This gave us the onset times of the vocalizations heard during the Listen phase which were imported into Scan software as an event file (.ev2) to mark as events for ERPs . This was repeated for all 150 vocalizations.

ERP Quantification

The N100, P300 and MMN ERP components were quantified.

N100. The auditory ERP N100 was elicited by the sound of a speaker's voice in the Talk-Listen paradigm. The ERPs were referenced to mastoid electrodes. Using the event file from voice analysis, ERPs were segmented into epochs from -100 ms to 500 ms. They were baseline corrected by using the time from -100ms to 0ms and a 1-30 Hz band-pass filter was used. They were baseline corrected again and artifact rejection (at electrodes VEO and HEO) was performed. Average ERPs were created for Talk and Listen conditions by averaging across all trials, respectively. A cut off of 80 accepted talk / listen trials was used to include a participant in further analysis.

Peak amplitudes were computed as the most negative deflection between 80 ms and 120 ms post stimulus at Fz, FCz and Cz for both Talk as well as Listen conditions. Peak amplitude and peak latency were exported for statistical analysis.

P300 and MMN. P300 and MMN ERP components were elicited in the oddball paradigm in response to the deviant stimulus. The ERPs were referenced to mastoid electrodes and then segmented into epochs from -100 ms to 500 ms. They were baseline corrected by using the time from -100ms to 0ms and a 1-30Hz band-pass filter was used. They were baseline corrected again and artifact rejection (at electrodes VEO and HEO) was done, prior to averaging. ERPs in response to the deviant stimuli were averaged to get the P300 waveform. Next, ERPs in response to the standard stimuli were subtracted from ERPs in response to the deviant stimuli (D-S) to get the MMN. A cut off of 120 accepted deviant trials was used to include a participant in further analysis.

Peak amplitude for P300 was computed as the most positive deflection between 250 ms and 500 ms at Fz, Cz and Pz. Peak amplitude for MMN was computed between 100-250 ms post stimulus at Fz and Cz.

Statistical Analysis

Spearman's correlations were done to assess the association between the questionnaire scores and the peak amplitude and latency of the ERP components (N100, P300 and MMN). For further assessment, participants were divided into a high-risk group and a low-risk group according to the questionnaires' guidelines and mixed between-within subjects analysis of variance was conducted. For the Talk-Listen experiment, the between subjects factors were risk (high and low) and gender. The within subjects factor was phase (talk and listen) and electrodes. For the Oddball experiment, the between subjects factors were risk (high and low) and gender. The within subjects factors were experiment (short deviant tone and long deviant tone) and electrodes. The analysis was conducted twice, once for each questionnaire.

Furthermore, Pearson's correlations were done to assess the association between P300 and MMN from the oddball experiment and the N100 suppression from the Talk-Listen experiment. Multiple regression analyses were then conducted using a combination of ERP components. N100 from the Talk-Listen experiment and the P300 and MMN from the oddball experiment were assessed in hierarchical regression analysis to determine the predictability of the questionnaire scores.

RESULTS

Fifty-eight right-handed Psychology undergraduates (Mean age 19.2 yrs; SD 2.0) participated in our study. Figure 2 shows the distribution of questionnaire scores of the participants. The Prime Screen and YPARQ-B questionnaires were positively correlated

($r=.898$, $p<.001$). Prime Screen had a maximum attainable score of 72 and the lowest was

0. Eleven participants scored 0 and one scored the maximum of 53 in our population,

while the rest of the scores ranged between these two values. YPARQ-B had a maximum

attainable score of 28 and a minimum of 0. Sixteen students attained a 0 and two scored

16, while the rest of the participants ranged between these values. It should be noted that

only significant and near significant results are mentioned and discussed. Also, Wilks'

Lambda and its associated significance has been reported in the results for mixed

between-within subjects ANOVAs. The partial eta squared value has been reported to

denote the effect size. Lastly, for each ERP component, the results for Prime Screen are

mentioned first and then for YPARQ-B consistently throughout this document.
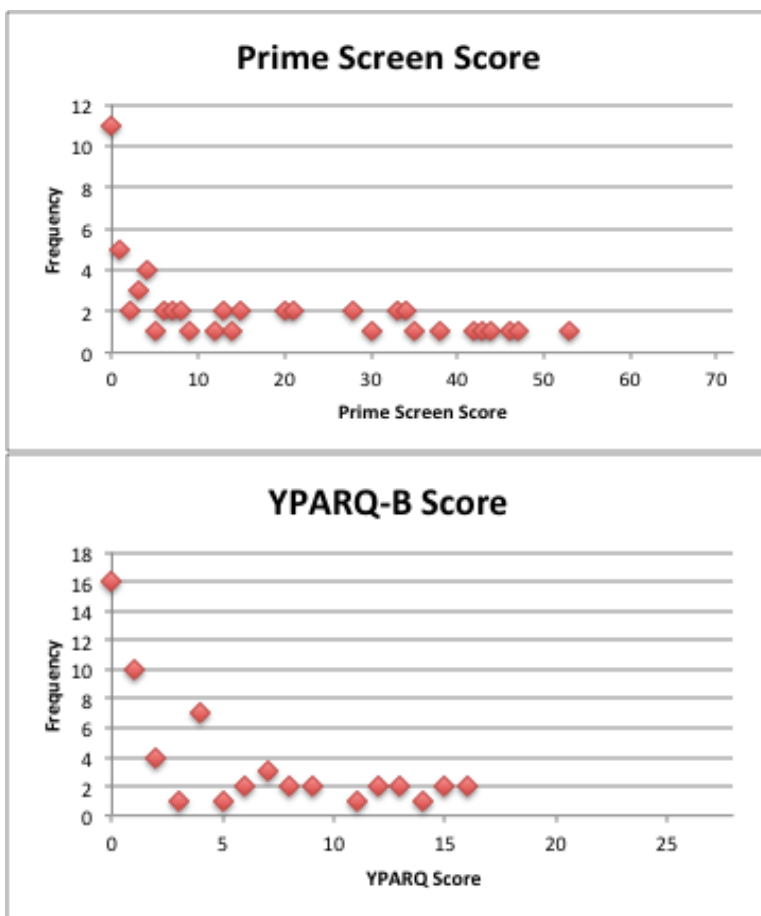
Figure 2. Distribution of the scores of Prime Screen and Youth Psychosis At-Risk

Questionnaire-brief (YPARQ-B).

Talk-Listen Experiment

Spearman's Correlations. To assess ERP differences across the continuum of

psychosis symptoms, Spearman's correlations were conducted. N100 suppression was

calculated by subtracting the N100 amplitude of the Listen phase from the Talk phase.

The N100 suppression effects did not significantly correlate with the scores on the

questionnaires. Although not significant, N100 suppression was negatively correlated

with risk for psychosis.

N100 Suppression. Since significant correlations weren't found, the participants

were divided into 2 groups on the basis of their scores. A person with one or more

'Definitely Agree' or three or more 'Somewhat Agree' in the Likert type Prime Screen

questionnaire is categorized as high-risk positive. Likewise, a score of 11 or more

categorizes an individual as high risk in YPARQ-B.

One-way ANOVAs assessed N100 suppression across the two groups for each

questionnaire separately. Although statistically not significant, risk of psychosis appeared

to be related to higher N100 amplitudes (lower N100 suppression) during talking in the

high-risk group, as compared to the lower risk group across both questionnaires.

A mixed between-within subjects analysis of variance was conducted to assess the

impact of risk of psychosis and gender on the N100 amplitudes in the talk and listen

conditions across Fz, FCz, Cz and the mean of the three electrodes. This was done

separately for each questionnaire to assess the influence of the risk for psychosis as

represented by the questionnaires' scores. Bonferroni adjustment to the alpha level was applied to judge statistical significance. A stringent alpha of .025 was obtained by dividing .05 by 2 (since we had two questionnaires) and used to assess significance for our comparisons. There was a statistically significant difference in N100 amplitudes between the two phases, Wilk's Lambda = .793, $F_{(1,27)}$= 7.037, p = .013, partial eta squared = .207, as expected when participants were categorized into positive and negative risk according to the Prime Screen (Figure 3). There was also a near significant main effect of electrode, Wilk's Lambda = .759, $F_{(2,26)}$=4.118, p=.028, partial eta squared = .241. The interaction of phase and risk was statistically significant, Wilk's Lambda = .760, $F_{(1,27)}$=8.526, p=.007, partial eta squared = .240. Also, the interaction of phase and gender was significant, Wilk's Lambda = .753, $F_{(1,27)}$= 8.870, p = .006, partial eta squared = .247. The interaction of phase and electrode was significant at Wilk's Lambda = .742, $F_{(2,26)}$= 4.531, p = .020, partial eta squared = .258 and the means show that the electrode with the most prominent difference in talking and listening was Cz.
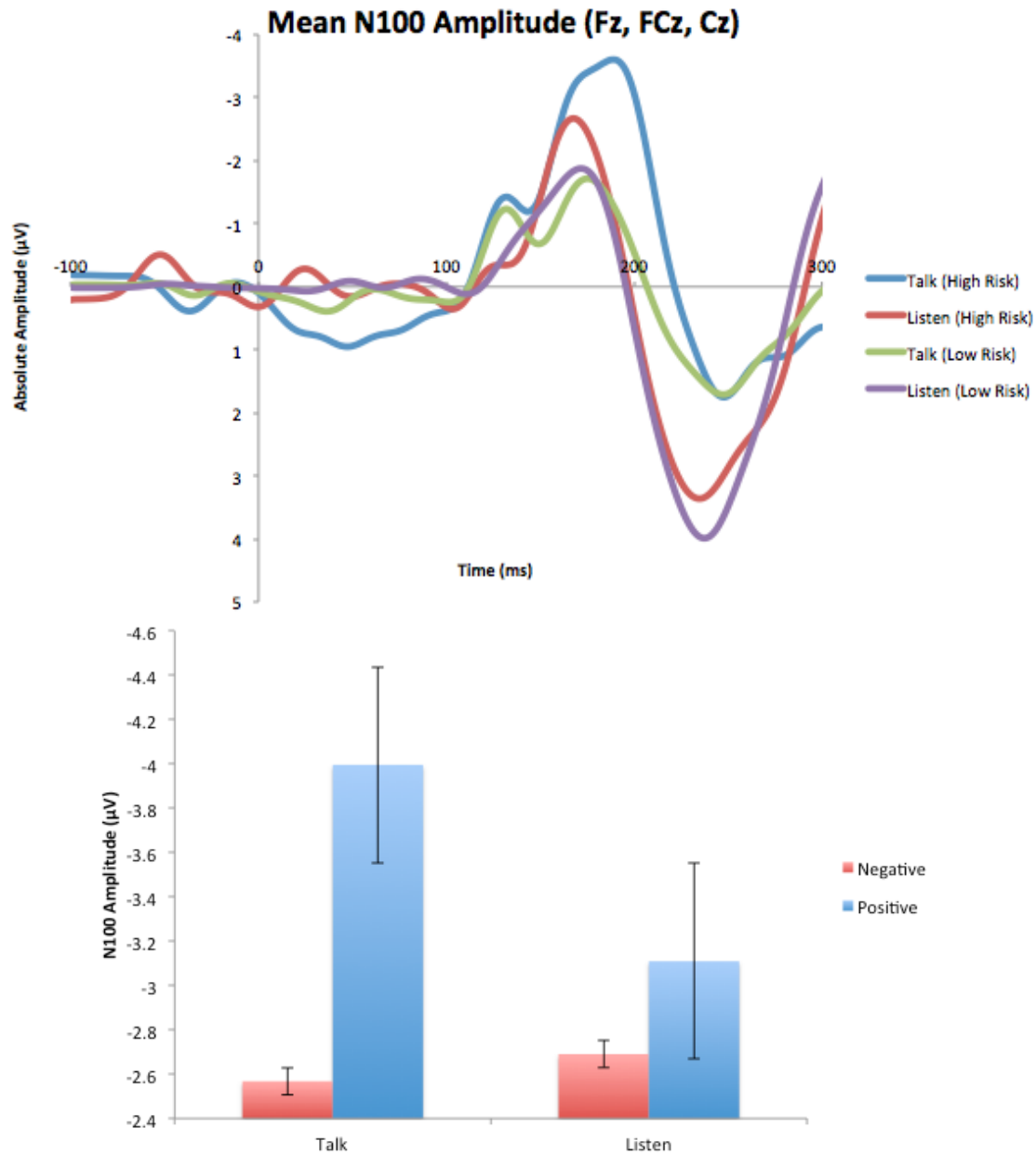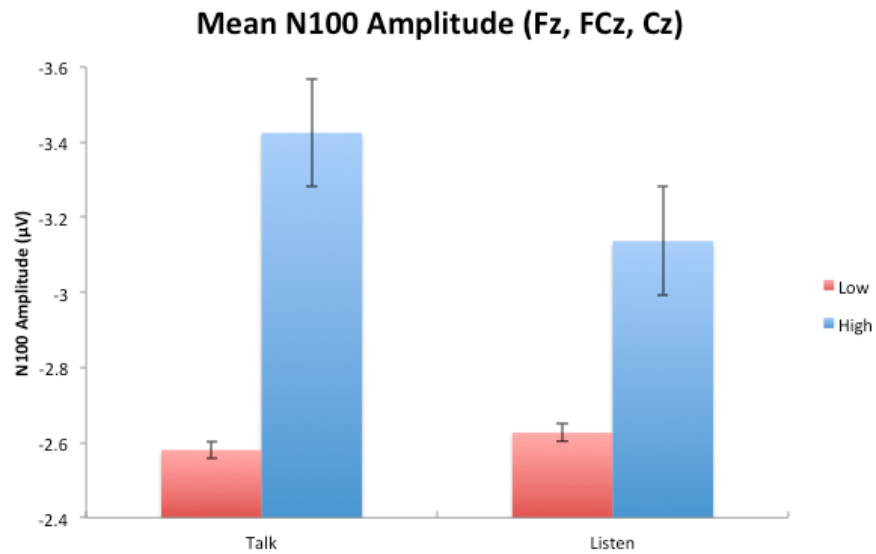
Figure 3. Mean N100 amplitude across Fz, FCz and Cz during talk and listen phases in high risk and low risk groups (Prime Screen).

A mixed between-within subjects ANOVA for YPARQ-B showed a significant interaction of phase and electrode, Wilk's Lambda = .616, $F_{(2,26)}$= 8.11, p = .002, partial eta squared = .384. However, using YPARQ-B did not yield any more significant results

when tested across its' high and low risk groups. Despite the non-significant results, the graph for the N100 amplitude at Fz showed a trend that was in the hypothesized direction (Figure 4).

Figure 4. Mean N100 amplitude across Fz, FCz and Cz during talk and listen phases in high risk and low risk groups (YPARQ-B).

Oddball Experiment

Spearman's Correlations. To assess P300 and MMN amplitudes across the continuum of questionnaire scores, Spearman's correlations were performed, similar to the Talk-Listen experiment analysis. In the first half of oddball experiment where a shorter 100 ms deviant tone was used, there were no significant correlations for either questionnaire. In the latter half of oddball experiment where a longer 150 ms deviant pure tone was used, there was a marginally significant relationship between MMN latencies at Fz ($r=-.296$, $p=.054$) and scores on the YPARQ-B. No other correlations were significant.

P300. To assess the effect of risk on P300 ERP and the extent to which the two different durations of the deviant tone had an effect on the P300 waveform, a mixed between-within subjects ANOVA was formulated. The main effect of electrode for P300 was statistically significant, Wilk's Lambda = .456, $F_{(2,24)}=14.316$, p<.001, partial eta squared = .544, when using Prime Screen to divide into a high and low risk group (Figure 5). Similarly, the main effect of electrode for P300 was statistically significant, Wilk's Lambda = .457, $F_{(2,24)}=14.264$, p<.001, partial eta squared = .543, when using YPARQ-B to divide into a high and low risk group.
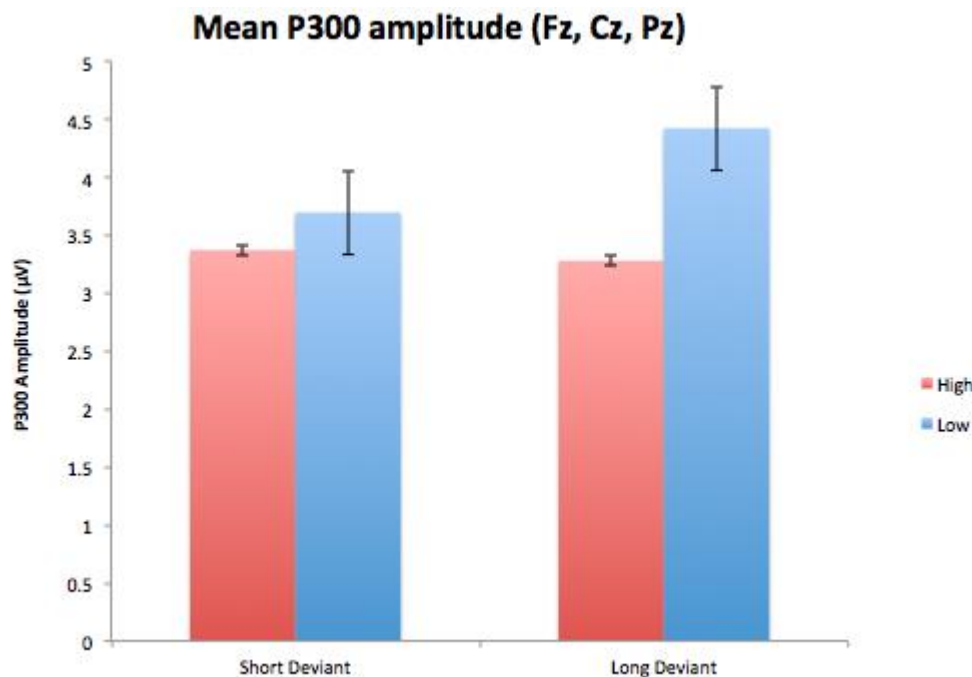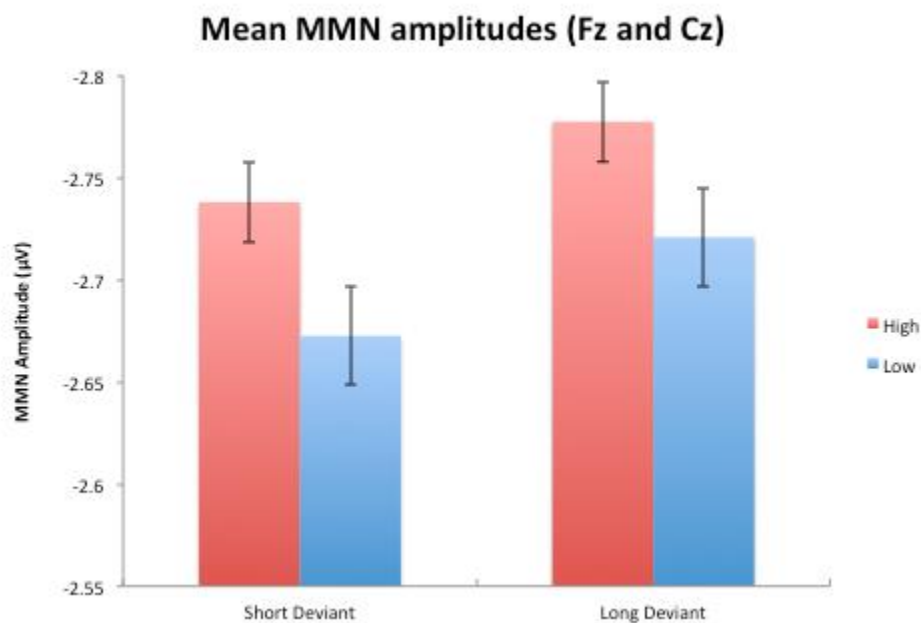

Figure 5. Mean P300 amplitude across Fz, Cz and Pz during short and long deviant oddball tasks in high risk and low risk groups (Prime Screen).

MMN. To assess the effect of risk on MMN ERP and the extent to which the two different durations of the deviant tone had an effect on the amplitude of the ERP, a mixed

between-within subjects analysis was conducted. The main effect of electrode for MMN was statistically significant, Wilk's Lambda = .742, $F_{(1,34)}$=11.806, p = .002, partial eta squared = .258, when using Prime Screen to divide into a high and low risk group. Similarly, when using YPARQ to divide into a high and low risk group, the main effect of electrode for MMN was statistically significant, Wilk's Lambda = .586, $F_{(1,34)}$=23.980, p<.001, partial eta squared = .414. Also, the two-way interaction of experiment and risk shows a marginal significance of Wilk's Lambda = .909, $F_{(1,34)}$=3.419, p = .073, partial eta squared = .091 (Figure 6).

Figure 6. Mean MMN amplitude across Fz and Cz during short and long deviant oddball tasks in high risk and low risk groups (Prime Screen).

Combined Results

To assess a relationship, if any, between the different ERP components across the oddball and the talk-listen paradigms, Pearson's correlations were conducted. P300

amplitudes in the oddball task at Fz, Cz, Pz and the mean of the amplitudes across the

three electrodes were used to run correlations with N100 amplitudes in the talk-listen

experiment at Fz, FCz and Cz. P300 amplitudes at Fz in response to the long (150 ms)

deviant tones significantly correlated with N100 suppression effects at Fz (r=.453,

p=.023), FCz (r=.480, p=.015) and Cz (r=.422, p=.036). P300 amplitudes at Pz in

response to long (150 ms) deviant tones showed a relationship with N100 suppression

effects at Fz (r=.341, p=.076), FCz (r=.380, p=.046) and Cz (r=.321, p=.096). Similarly,

mean of P300 amplitudes at Fz, Cz and Pz in response to long (150 ms) deviant tones

correlated significantly with N100 amplitudes at Fz (r=.409, p=.028), FCz (r=.434,

p=.019) and Cz (r=.380, p=.042). P300 amplitudes in response to short (100 ms) deviant

tones at electrodes Fz, Cz and Pz did not correlate with any N100 value.

Next, MMN amplitudes at Fz, Cz and their mean in the oddball experiment were

correlated with N100 suppression values at the Fz, FCz and Cz electrodes in the talk-

listen experiment. MMN amplitudes at Fz in response to short (100 ms) deviant tones

were significantly correlated with N100 suppression values at Fz (r=-.371, p=.052), FCz

(r=-.415, p=.028) and Cz (r=-.377, p=.048). Mean MMN amplitudes also showed

significant correlations with N1 at Fz (r=-.341, p=.076), FCz (r=-.386, p=.043) and Cz

(r=-.346, p=.071). MMN in response to the long (150 ms) deviant tones were not

significantly correlated with N100 values at any electrode.

Risk Predictability

As a follow-up, multiple linear regressions were performed to assess the degree to

which ERPs could predict the risk of psychosis. P300 amplitudes across Fz, Cz and Pz

accounted for 40.4% of the variance in Prime Screen scores ($F_{(3,16)}=3.614$, p=.036) and 45.9% of the variance in YPARQ-B scores ($F_{(3,16)}=4.518$, p=.018). MMN amplitudes accounted for 27.5% of the variance in YPARQ-B scores ($F_{(2,25)}=4.739$, p=.018), whereas the MMN amplitudes were not significantly predictive of Prime Screen scores. Similarly, N100 amplitudes were not predictive of either questionnaire.

P300 & N100. To evaluate the risk predictability strength of a combination of ERP components, we did hierarchical multiple regression analysis of the ERP components from the Oddball and the Talk-Listen experiments. P300 amplitudes from the oddball experiment and N100 suppression values from the Talk-Listen experiment were tested first. They were analyzed as two blocks in hierarchical regression. As mentioned previously, P300 alone was 40.4% predictive of Prime Screen scores. N100 alone was not significantly predictive of either questionnaire. However, when tested together N100 suppression explained an additional 25.7% ($F_{(6,13)}=4.220$, p=.014) of the variance in the Prime Screen questionnaire scores, even when the effect of P300 was statistically controlled for. On the other hand, P300 alone accounted for 45.9% of the variance for the YPARQ-B, as mentioned previously. Though N100 alone was not significantly predictive, the variance accounted for by the N100 as part of a combination analysis was marginally significant at 8.5% ($F_{(6,13)}=2.583$, p=.072) for YPARQ-B scores.

MMN & N100. Furthermore, MMN amplitudes and N1 suppression values were analyzed as two blocks in a multiple hierarchical regression. These two components were not significantly predictive of Prime Screen scores. On the other hand, MMN was 27.5% predictive of YPARQ-B scores ($F_{(2,25)}=4.739$, p=.018), as mentioned previously. N100

amplitudes explained a further 5.2% of the variance in YPARQ-B scores ($F_{(5,22)}$=2.133, p=.099).

P300 & MMN. Lastly, P300 and MMN amplitudes were tested as two blocks in hierarchical regressions as well. P300 amplitudes explained 40.4% ($F_{(3,16)}$=3.614, p=.036) of the variance and MMN amplitudes explained 6.4% ($F_{(5,14)}$=2.461, p=.085) of the variance in Prime Screen scores when part of a combination analysis. Similarly, 45.9% ($F_{(3,16)}$=4.518, p=.018) of the variance was explained by P300 amplitudes and 8.3% ($F_{(5,14)}$=3.311, p=.035) of the variance was explained by MMN amplitudes in YPARQ-B scores.

Supplementary analysis

Further analysis was conducted using mean amplitudes of the ERP components instead of the peak averages. Also, analysis was conducted using data from participants at the extreme ends of the scores to assess if a more pronounced difference between the high risk and the low risk groups was observed in our population. Since, the overall pattern of results was similar, the results for the supplementary analysis were not included.

DISCUSSION

The focus of the current study was to assess whether variations in ERP components are related to risk for psychosis in order to identify an ERP marker associated with non-clinical psychotic symptoms. The data show that certain ERP

variations in the populations are related to an individual's place along a psychosis

continuum. By using two paradigms previously shown to elicit ERPs that are predictive

of schizophrenia, we were able to explore, the combinative power of these previously

known endophenotypic markers for psychosis for predicting prodromal symptoms of

psychosis. In the talk-listen paradigm, the N100 amplitudes during talking were reduced

as compared to listening. Furthermore, there were higher N100 amplitudes (reduced

N100 suppression) during talking as compared to listening in the group with higher risk

for psychosis. In the second experiment, participants completed an oddball task in which

a series of standard tones were presented. Duration deviant tones elicited P300 and

mismatch negativity waveforms. The P300 and mismatch negativity amplitudes did not

significantly relate to risk for psychosis. Also, risk predictability assessment was

conducted using combinative analytic power from both experiments. We concluded that

risk was associated with ERP components in our population, and a combination of

oddball and talk-listen experiment provided better risk predictability than either of them

alone.

Talk-Listen experiment

During the Talk-Listen task, we expected that N100s would be elicited in response to

listening to a pre-recorded 'ah', irrespective of risk for psychosis. However, based on

previous research (Ford et al., 2013), we expected that the N100 amplitudes would be

suppressed while participants vocalized. Additionally, we proposed that the N100

suppression effects would correlate with the risk for psychosis, as indexed by the scores

on the risk assessment questionnaires. As expected, N100 amplitudes were suppressed

during the talk phase as compared to the listen phase. However, contrary to our expectations, the N100 suppression during the talk phase was not correlated with the risk for psychosis.

There are several possible reasons that we did not observe a correlation between N100 suppression and the risk scores on the questionnaires. First, like many other researchers have observed when surveying a general population, our participants' scores were skewed toward the low end of risk for psychosis across both the Prime Screen and YPARQ-B questionnaires. These skewed scores could be the reason why risk for psychosis is not normally distributed within healthy populations. Moreover, since the data were collected all semester long from undergraduate students confounding variables such as exam stress may have caused some participants to score higher on the risk assessment scales than they would under less stressful periods of life. An alternate explanation, however, for the distribution of responses on our questionnaires is that the primary goal for these risk-assessment questionnaires is to 'screen out' at-risk individuals (Kline et al., 2012). Therefore, the questionnaires may not be adequate to assess people across a continuum for psychosis risk. Regardless of the source of this restricted range, determining a trend between the risk of psychosis and N100 suppression, as well as any of our other ERPs of interest may have been affected.

Failure to obtain significant correlations prompted us to divide participants into a higher and lower risk group based on the scores. Previous studies (Broyd et al., 2016) that did not find significant correlations across the continuum of risk for psychosis have also divided participants into high and low risk groups. However, previous studies used a simple median split to create the high and low risk groups, while we used the

recommended score ranges for the respective questionnaires to differentiate between the high and low risk groups. This, we hoped, would produce more accurate results because a median split of our data would mean that a participant who scored 9 on the YPARQ-B questionnaire, for example, would be included in the high risk group when the questionnaire clearly specifies 11 or more as high risk. Using a median split then would prevent us from using the recommended guidelines for evaluating risk for each questionnaire. That said, although one-way ANOVAs assessing N100 suppression did not yield significant results, N100 amplitudes were higher (lower N100 suppression) during talk condition for the high-risk group, as compared to the lower risk group as assessed by both questionnaires. And, since there was a main effect of phase using the Prime Screen to divide into two groups, N100 amplitudes were more positive (suppressed) during the Talk phase as compared to the Listen phase, regardless of risk to psychosis. This is expected, as healthy individuals suppress the sensation of action to mark a particular action, in this case vocalizing 'ah,' as self produced (Ford et al., 2013). Furthermore, the significant interaction between phase and risk is indicative of a reduced N100 suppression (higher N100 amplitude during talking) in individuals at higher risk of psychosis. As the population tested here is healthy with no clinically evident symptoms of psychosis, this pattern of results implies that there is some degree of suppression of N100 amplitude during talking even in people in the early prodromal stage. There were multiple significant gender interaction effects but since the sample size was small, gender factor was not looked into deeply.

The mostly non-significant results that we observed when the YPARQ-B (in contrast to Prime Screen) scores were used to divide the sample into the high and the low

risk groups may be indicative of the sensitivity of the questionnaire itself. Prime Screen has repeatedly been shown to be more sensitive than the YPARQ-B (Addington et al., 2015). Our results support this as well. If our hypotheses are correct and the N100 provides some predictive value regarding psychosis, then our observation that dividing our participants into high and low risk groups on the basis of their Prime Screen yielded significant differences in their ERP amplitudes supports the Prime Screen as the more effective questionnaire. Thus, it is possible that certain individuals were falsely categorized as high risk on the basis of the YPARQ-B questionnaire scores. Indeed, previous research that showed YPARQ-B to be an effective screening measure recruited participants from help-seeking outpatients or individuals referred to a high-risk clinic (Kline et al., 2012) instead of a general population, which was the population recruited for this study. It should also be noted, however, that Prime Screen and YPARQ-B are both based on the attenuated positive symptoms approach and tap into the late prodromal symptoms. An improved approach would have been to incorporate a questionnaire based on the basic symptoms approach. As well, we cannot rule out the role of confounding variables such as exam stress and time of testing. However, participants that were categorized as high risk on the basis of YPARQ-B did have higher N100 amplitudes (though not significantly so) during the talking phase compared to the listening phase, thus it is possible that a larger sample size would show similar effects with the YPARQ-B as a risk assessment tool.

Oddball experiment

We expected P300 amplitudes and MMN amplitudes to become significantly smaller as risk increased. However, P300 and MMN amplitudes did not correlate

significantly in the expected direction with the scores on the questionnaires. Similar to

the correlations for the Talk-Listen experiment mentioned earlier, this may in part be

explained by the skewed scores of the questionnaire. On the other hand, MMN latencies

at Fz showed a trend-level negative correlation with YPARQ-B. In other words, as the

score on the questionnaire increased, i.e. as the risk for psychosis increased, the MMN

latency decreased. A shortened MMN latency is in line with previous research (Kargel et

al., 2014) and indicates defective early processing of incoming stimuli that may introduce

errors in the received information. A short latency reduces the time that is required to

efficiently integrate incoming stimuli with the pre-existing schema in the brain (Grzella et

al., 2001). This eventually affects cognitive functioning (Kargel et al., 2014), and

cognitive impairment is a symptom of psychosis (Baldeweg et al., 2004).

In a healthy population, hearing deviants with different durations than the

standard stimulus elicits MMN and P300 ERP responses (Murphy et al., 2013; Simons et

al., 2011). Longer duration deviants cause larger MMN responses (Pakarinen et al.,

2007). Two durations for the deviants in the 60 ms / 100 ms (short deviant) and the 60 ms

/ 150 ms (long deviant) oddball experiments were therefore used to identify any effects of

increasing the duration of the deviant stimulus on the amplitude of P300 and MMN.

Previous researchers have hypothesized that the brain's estimation of error size in people

with psychosis is atypical, so our objective was to determine whether any differences in

the relative difference in the magnitude of the MMN amplitudes observed for the short

and long deviant tones in the oddball experiments varied depending on risk for psychosis.

Our results showed that the interaction of experiment and risk had a *p* value of .073.

Although not significant, this near significance suggests that the increase in the

magnitude of deviance from 100 ms to 150 ms, may increase the MMN amplitudes in

low risk individuals. This is consistent with prior research in healthy populations where

significant differences for MMN amplitudes were observed in response to different

magnitudes of duration deviance (Pakarinen et al., 2007). However, increasing the

duration of deviance from 100 ms to 150 ms, may show no difference in the MMN

amplitude in high risk individuals. To the best of our knowledge, this was the first study

to assess effects of multiple magnitudes of deviant stimuli with reference to schizotypy. It

is possible that a 50% increase in deviance from 100 ms duration for one deviant to 150

ms for the other deviant is too prolonged an increase in the length of deviant magnitude

to observe a significant difference in ERP amplitudes and validate our hypothesis. It

would be interesting to study MMN amplitudes by employing a smaller increase in

deviant tone duration (for instance a duration of 120ms), since duration deviant

magnitudes that were employed in a previous study in a healthy population (Pakarinen et

al., 2007) were varied in steps of 8 ms from the standard tone.

Combined Results

Given the between and within participant variability often observed for single ERPs,

we hypothesized that using two or more ERPs previously shown to differ between a

healthy population and a population of individuals with schizophrenia would provide

more predictive power when predicting risk for psychosis. For this reason, we tested the

relationship between P300 amplitudes from an auditory oddball experiment and N100

suppression effects from the Talk-Listen paradigm. Significant correlations between P300

amplitudes at Fz (in response to 150 ms deviant tone) and N100 suppression effects

across Fz, FCz and Cz were observed. It should be noted here that the P300 at Fz

electrode showed the highest correlations, which seems logical since automatic attention

is localized to the frontal region. This significant correlation between P300 amplitudes

and N100 suppression shows that smaller brain responses elicited during the oddball

experiment were related to smaller brain responses in the Talk-Listen experiment.

Critiques of this notion of correlating different ERP components across two separate

experiments may argue that the whole idea is redundant since the underlying cause for

poor performance in both experiments is being at-risk for psychosis. As risk increased,

there was a certain degree of cognitive impairment that was responsible for the reduced

P300 amplitudes and reduced N100 suppression (increased N100 amplitude) during

talking. But it should be emphasized here that in contrast to N100 suppression and P300

amplitudes in response to long deviant tones (60 ms / 150 ms oddball task), which

showed a significant relationship, N100 suppression values did not significantly correlate

with P300 amplitudes in response to short deviant tones (60 ms / 100 ms oddball task).

This is important to mention since a larger deviance magnitude requires longer attentional

processing. It is possible that P300 amplitudes in response to longer deviant tones shows

deficit earlier and then as psychosis proneness increases there is further deficit in P300

amplitude in response to a short deviant tone when tested in at-risk population. Yet, most

previous literature used shorter durations (Murphy et al., 2013; Nagai et al., 2013b;

Bodatsch et al., 2011) than the durations used in this study and none have employed two

different magnitudes of duration deviant tones in an at-risk population. Consequently,

this shows that using such stimuli in oddball paradigms alongside Talk-Listen experiment

is a better approach to identify high-risk persons.

Negative correlations between MMN amplitudes and N100 suppression values indicated that as the MMN voltage (reduced MMN amplitude since it is a negative waveform) increased, the N100 suppression became more negative (high N100 amplitudes during talking). Since N100 suppression was calculated by subtracting N100 amplitudes of the listen phase from the talk phase, more negative values means that the as amplitude increased in the talk phase, N100 suppression was reduced during talking. This suggests that the participants with reduced MMN amplitudes also had reductions in N100 suppression. This indicates that cognitive processes responsible for generation of MMN as well as N100 are impaired and using both components provides better accuracy in placing individuals on the psychosis continuum than either of them alone.

Assessing risk predictability using hierarchical multiple regressions enabled us to understand how well a score on the questionnaire can be predicted using a combination of ERP components. This also sheds light on the accuracy of the questionnaires used. In the P300 and N100 risk predictability analysis, N100 suppression values did not account for any variance on the questionnaire on their own. However, when combined with P300, N100 suppression accounted for 25.7% of the variance in the Prime Screen score. This further signifies the importance of combining these two ERP paradigms for risk identification and analysis. The combination of MMN and N100 suppression had marginal significance for YPARQ-B score predictability in the hierarchical regression analysis. It is possible that a larger sample size would better assess the predictive power of this combination of ERP components. Lastly, the P300 and MMN amplitudes were regressed together, the MMN accounted for 8.3% of variance in YPARQ-B score while the P300 accounted for 45.9% of the variance. One worthwhile observation was that

P300 amplitudes best predicted questionnaire scores among the three ERP components. This finding is in line with research that shows that P300 amplitudes decline during the prodromal period and are at their minimum at the onset of the first episode of psychosis (Devrim Üçok et al., 2016), quite unlike the other two ERP components tested here. Moreover, P300 amplitudes have been observed to correlate with negative symptoms of schizophrenia (Mathalon et al., 2000) and as a result it may be unsurprising that the P300 amplitude would be the first ERP component to show a relationship to negative symptoms that occur prior to the first episode of psychosis.

General Discussion

This study provided an assessment of ERP variations across a continuum of psychotic symptoms in non-clinical population using two well-established paradigms. Our aim was to identify the ERP component or combinations of ERP components that best predict risk for psychosis. The results suggest that although one ERP component may correlate with risk, a combination of ERPs might actually be more predictive of schizotypy during the psychosis prodrome. The oddball and Talk-Listen paradigms may in fact identify at-risk individuals earlier along the psychosis continuum than either of them alone.

P300

In this study, the P3a was elicited by means of the passive oddball task. The rationale for assessing P3a instead of P3b was to be able to accommodate P300 and MMN in one experiment since automatic P300 (P3a) requires a paradigm without overt responses and

the MMN can be elicited by an automatic task. Our aim was to test the P300, MMN and

N100 in one experimental session that was of a reasonable duration. As environmental

stress directly influences psychosis vulnerability, testing an individual during a time of

financial stress, for instance, can show different results than times without stress.

However, it must be noted that an oddball experiment that included a button press

response for participants to indicate that they had detected deviant tones would also be an

ideal task to assess P300 since effortful attention (P3b) is also predictive of diagnosis of

psychosis (Ford et al., 1996). Another possibly effective task may be to incorporate a rare

white noise burst in an oddball experiment for which no button response is required while

incorporating a deviant tone with button responses so as to combine automatic and

effortful attentional processes in a single paradigm (Ford et al., 1996). Participants can

then be instructed to respond to the duration deviant tone with a button press (P3b) while

ignoring the white noise (P3a).

The results of this study suggest that a relatively large difference between the

standard and deviant stimuli in an oddball experiment may be required to show

significant correlations between the P300 and N100. P300 amplitudes in response to long

deviant tones were significantly correlated to N100 suppression effects, but no significant

correlations between P300 amplitudes in response to short deviant tones and N100

suppression values were observed. This may mean that larger differences between

standard and deviant stimuli will be needed to provide better risk predictability when

combined with other tasks. It is possible that individuals who experience early psychosis

vulnerability show reduced P300 amplitudes in longer attention demanding tasks. As

their proneness to psychosis increases, they start to elicit attenuated P300 waveforms in

response to tasks that require attention for lesser durations of time as well. It is worth investigating by using multiple deviant magnitudes for frequency and intensity of tones to further study this supposition.

MMN

A trend level interaction between the mean MMN amplitudes and scores for the risk of psychosis gives tentative support for our hypothesis that there are lower MMN amplitudes during oddball tasks in higher risk individuals. Although a previous study of MMN in persons ranking high on schizotypy (Broyd et al., 2016) showed no significant MMN amplitude reduction in high-risk individuals, one of the explanations provided by previous researchers was that these high schizotypy individuals were non-converters to psychosis. Perhaps, MMN is a marker of conversion to psychosis and the individuals tested here are mostly non-converters and this is the reason for our trend level interactions. It would be worth following up individuals in our study to observe if they develop psychosis later in life.

The mean MMN waveform across all participants showed a double peak that corresponds to the two underlying processes as proposed by the model adjustment hypothesis for MMN generation: the sensory memory mechanism in the temporal area and the attention switching mechanism occurring in the prefrontal region. The existence of these two underlying processes was supported earlier by an fMRI-EEG study (Doeller et al., 2003) that showed double peaks in the fronto-temporal brain regions. This finding was replicated in our study. However, it should be noted that double peaks for MMN were observed in response to the short deviant tones (60 ms / 100 ms oddball task) only. Interestingly, the MMN waveform in response to the long deviant tone (60 ms / 150 ms

oddball experiment) showed a single peak for MMN. It is possible that the attention switching mechanism, which is denoted by the latter peak, is enhanced enough in response to the long deviant tone that the smaller first peak is 'consumed' into the second peak and shows as a single peak. Nevertheless, this explanation needs further backing up for validity.

Lastly, increasing the duration of the deviant tone from 100 ms to 150 ms showed marginally significant effects on the MMN amplitudes, which suggests that as magnitude difference between standard and deviant stimuli increases, there is an increase in MMN amplitudes. This means that a larger difference between the standard and deviant stimuli elicit larger MMN amplitudes, which is consistent with the pattern observed in previous literature (Pakarinen et al., 2007). However, incorporating complex variants of the oddball paradigm would help in understanding this effect further.

One possible confound for our study is the relationship between smoking and MMN amplitudes. It is known that people that smoke have significantly increased MMN amplitudes compared to their non-smoking counterparts (Kargel et al., 2014). At a neurochemical level, nicotine in cigarettes has a cholinergic effect that is known to affect cognition (Kargel et al., 2014). Also, the prevalence of smoking in schizophrenia is nearly four times higher than in normal population (Kumari & Postma, 2005). Thus, the prevalence of smoking among individuals prone to psychosis could likewise be higher than the general population. As we did not take smoking behaviour into account, differences in smoking may be a confounding factor for our study.

N100

The significant reduction of N100 amplitudes in talking as compared to listening

supports the proposition that an efference copy/corollary discharge mechanism is used to

compare the predicted and the actual feedback to dampen the sensation of action (Ford et

al., 2013). In healthy individuals, this efference copy / corollary discharge mechanism

helps to distinguish between self and the outside world (Ford et al., 2013). However,

higher risk individuals showed increased N100 amplitudes during talking (reduced N100

suppression), which suggests that individuals that rank high on schizotypy do not show

this N100 suppression to the same degree as healthy individuals. These findings are

consistent with studies that show increased activity in the temporal lobe instead of

decreased activity during speech in individuals with auditory verbal hallucinations

(Oestreich et al., 2015a). It should be noted, however that our population shows no

apparent symptoms of psychosis or considerable cognitive impairment that may affect

everyday life or that has caused them to seek medical help. Perhaps, the N100

suppression impairment gradually progresses over time until they are unable to

distinguish between self and the outside world, eventually resulting in hallucinatory

behaviour. This is in line with our hypothesis that the variations in ERPs are directly

affected by risk and are measurable before clinically evident symptoms.

Implication in Clinical Practice

Pharmacotherapy and psychosocial interventions are a mainstay of treatment in

psychosis (First & Tasman, 2011). The goal is to actively manage symptoms with the

best possible intervention and to reduce the duration of untreated psychosis (Cheng &

Schepp, 2016). The fundamental aim is to improve quality of life with the most suitable treatment approach. However, quality of life and prognosis of the disease is largely influenced by early diagnosis (Cheng & Schepp, 2016). Prompt diagnosis is made possible when very subtle prodromal symptoms are recognized early enough in clinics. We propose that a concise yet comprehensive EEG test based on a risk predictability model could be used to assess individuals who present even minor cognitive or social impairments. N100 from the Talk-Listen paradigm and P300/MMN from the oddball experiment may be elicited using various manipulations in multiple large-scale populations. Furthermore, replication of this study with enhancements that perfect the manipulation of the Talk-Listen and oddball tasks can be conducted and a battery of brief EEG tests involving multisensory ERPs may be formulated. This can then be implemented in clinics to identify the exact position along the psychosis proneness-persistence-impairment model and initiate a timely management protocol. This idea of a clinically practical protocol involving a battery of tests is similar to the one outlined by Kieffaber and colleagues (Kieffaber et al., 2016), who tested by means of a concise 20-minute oddball task involving eight different ERP components in the auditory as well as visual domain. If a series of ERP assessments could estimate time to transition to psychosis at the very least, it would be a breakthrough in psychosis treatment.

In a clinical setting, this combination of ERP tests has a potential of being a time saving diagnostic aid in schizophrenia and other psychoses. Its cost-effectiveness (in comparison to long term treatment and hospitalizations) and brevity can assist in it being a prospective large-scale risk-screening tool to identify vulnerable individuals early on and reduce morbidity.

Limitations and Future Directions

There were a few limitations in this study. Firstly, a study that tests a population across a continuum should ideally have a large sample size, since it is understandable that a sizable majority of individuals will score at the lower end of the continuum. Also, ensuring that there is sufficient data from participants across all scores of the scale assessing schizotypy, specifically participants who score toward the higher end of the continuum, would certainly assist in predictability of risk assessment. The aim of this study was to create a risk predictability model that could be applied in various platforms. Ideally, this study should be replicated on individuals that are clinically at-risk for psychosis, first episode psychosis patients and known schizophrenia populations. Risk analysis and predictability in first episode patients will help in identifying persons who would end up having extended clinical outcomes. Such further research on individuals all across the psychosis proneness-persistence-impairment continuum will validate this risk predictability model. Moreover, it would be beneficial if a longitudinal study could be conducted and persons who score high on the continuum could be followed up for at least 5-6 years since this is the average time span for a prodrome period to last before first episode of psychosis (Bodatsch et al., 2011). Furthermore, as it is known that there is gradual loss of cortical tissue even before onset of psychosis, it provides another reasonable purpose to follow-up such individuals. Cortical connectivity during oddball and Talk-Listen tasks is worth exploring since it is known that there are structural abnormalities in the cortical regions in psychosis (Ford et al., 1994).

Another limitation concerns the risk screening tools. Self-report questionnaires carry a certain amount of response bias and a social desirability bias (Krumpal, 2013). For a more optimum classification criteria, clinician rated questionnaires would be a better choice in our opinion. Also, since both Prime Screen and YPARQ-B were based on the attenuated psychosis symptoms approach and the target of this study was healthy population that was not seeking any medical help, it would have been better if a questionnaire with a basic symptoms approach was used. In this study, the recruitment was restricted to university students, which is an inaccurate representation of the general population. Incorporating education level, economic status and drug use in the analysis would show the effect of these variables, since environmental stress aggravates psychosis vulnerability and indirectly affects the performance in the assigned tasks.

Improved variations of the oddball task can be employed and the resulting P300 and MMN amplitudes can be combined with N100 suppression deficits to assess the predictive nature of these ERP components. Use of complex oddball paradigms, for instance, those that involve closely sounding phonemes can be employed, as it would require increased attentional processing. Since our study found that P300 amplitudes in response to longer deviant oddball task (in contrast to the shorter deviant oddball task) were highly correlated to N100 suppression effects, we expect complex oddball paradigms to provide better risk predictability. A reversed oddball paradigm can be employed in which the standard and deviant tones alternate after a series of trials and hence require greater effort from the higher cortical areas since the prediction model keeps updating. However, the disadvantage for that paradigm would be that for 50% of the trials the deviant would be duration decrement instead of duration increment deviant

tones. As mentioned earlier, the duration increment MMN is significantly attenuated in at-risk population in comparison to duration decrement MMN (Todd et al., 2013). This would mean that a larger number of trials would be required to get a sufficient number of duration increment trials using a paradigm in which the prediction model continuously updates. Additionally, this study could be replicated using intensity deviant tones since ERPs in response to intensity deviant tones get affected in a similar fashion as duration deviants i.e. in the prodromal period, as discussed earlier (Kargel et al., 2014): This would provide a valid comparison of the affected ERP components. Lastly, one improvement for the MMN oddball task would be to play a silent movie to make the task less boring (Horvath et al., 2008; Gaebler et al., 2015).

Improving the Talk-Listen paradigm would certainly be of value in risk assessment. Cued listen conditions can be incorporated alongside passive listening. The rationale behind cued listening is to remove the confound of predictability between the talk phase and the listen phase, as participants can predict their vocalization while talking (Oestreich et al., 2015b) in contrast to when they just passively listen to their recorded voice. The resulting N100 suppression effects would be devoid of the effect of temporal predictability, which would remove a potential confound in the risk assessment.

The aforementioned ERP effects have been individually studied within the auditory modality. However, using multiple ERP indexes for the risk of psychosis can also be applied in the multi-sensory domain. Neuhaus and colleagues (Neuhaus et al., 2013) first demonstrated significant reductions in visual MMN amplitudes in schizophrenia as compared to healthy individuals. Significant ERP reductions among clinically high-risk individuals in contrast to healthy controls have also been observed in

response to varying concentrations of odour (Kayser et al., 2013). Smell identification

deficits correspond to negative symptoms of psychosis (Kayser et al., 2013) and may

predict risk of conversion from the prodromal stage to clinical psychosis (Kotlicka-

Antczak et al., 2016). Likewise, in the tactile domain, individuals that are prone to

psychosis-like positive symptoms express an increased illusion of body ownership in the

rubber hand illusion (Germine et al., 2012). In this experiment, an individual's hand is

stroked with a brush at the same time he/she sees a rubber hand being stroked.

Schizophrenia patients feel the illusion earlier and stronger than healthy individuals

(Peled et al., 2000). That all being said, since we know that there is some degree of multi-

sensory integration dysfunction in psychosis (Stekelenberg et al., 2013), incorporating

ERPs across different sensory modalities (for example, a combination of visual, auditory

and tactile oddball experiments) may provide more comprehensive information in the

assessment of risk for psychosis. Another helpful direction in establishing this risk

predictability model is studying ERP alterations in other sensory domains. P300 and

MMN using tactile and visual oddball tasks can further help understand the pathway to

psychosis.

CONCLUSION

In summary, the findings of this study are consistent with an existence of a

continuum of psychosis measurable by risk assessing tools. The risk for psychosis

corresponds to respective ERP waveform abnormalities that can be assessed long before

characteristic psychotic symptoms appear. Attenuated P300 and MMN amplitudes in the

oddball experiment and higher N100 amplitudes while talking (reduced N100

suppression) in the Talk-Listen task are robust findings in individuals with psychoses,

even when tested separately. However, all three ERP components together with their

combinative analytic power may better predict risk in a general population. Nevertheless,

further research is required to replicate these findings on a larger sample size using

improved experiment manipulations to establish the risk predictability model. This would

allow efficient assessment of psychosis risk and may fulfill the necessity of an effective

way to diagnose psychosis earlier. This eventually may improve prognosis of psychotic

disorders and be a turning point in clinical practice.

<u>References</u>

Addington, J., Stowkowy, J., & Weiser, M. (2015). Screening tools for clinical high risk

for psychosis. *Early Intervention in Psychiatry*, *9*(5), 345–356.

https://doi.org/10.1111/eip.12193

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental

disorders* (5th ed.). Washington, DC: Author.

Atkinson, R. J., Michie, P. T., & Schall, U. (2012). Duration mismatch negativity and

P3a in first-episode psychosis and individuals at ultra-high risk of psychosis.

Biological Psychiatry, *71*(2), 98–104.

https://doi.org/10.1016/j.biopsych.2011.08.023

Baldeweg, T., Klugman, A., Gruzelier, J., & Hirsch, S. R. (2004). Mismatch negativity

potentials and cognitive impairment in schizophrenia. *Schizophrenia Research*,

69(2–3), 203–217. https://doi.org/10.1016/j.schres.2003.09.009

Bendixen, A., SanMiguel, I., & Schröger, E. (2012). Early electrophysiological indicators

for predictive processing in audition: A review. *International Journal of

Psychophysiology*, *83*(2), 120–131. https://doi.org/10.1016/j.ijpsycho.2011.08.003

Bodatsch, M., Ruhrmann, S., Wagner, M., Mller, R., Schultze-Lutter, F., Frommann, I.,

Brinkmeyer, J., Gaebel, W., Maier, W., Klosterkötter, J., & Brockhaus-Dumke, A.

(2011). Prediction of psychosis by mismatch negativity. *Biological Psychiatry*,

69(10), 959–966. https://doi.org/10.1016/j.biopsych.2010.09.057

Bottcher-Gandor, C. and Ullsperger, P. (1992), Mismatch Negativity in Event-Related

Potentials to Auditory Stimuli as a Function of Varying Interstimulus Interval.

Psychophysiology, 29: 546–550. doi:10.1111/j.1469-8986.1992.tb02028.x

Bramon, E., Rabe-Hesketh, S., Sham, P., Murray, R. M., & Frangou, S. (2004). Meta-

analysis of the P300 and P50 waveforms in schizophrenia. *Schizophrenia Research*,

70(2–3), 315–329. https://doi.org/10.1016/j.schres.2004.01.004

Broyd, S. J., Michie, P. T., Bruggemann, J., van Hell, H. H., Greenwood, L. marie, Croft,

R. J., Todd J., Lenroot, R., & Solowij, N. (2016). Schizotypy and auditory mismatch

negativity in a non-clinical sample of young adults. *Psychiatry Research -*

Neuroimaging, *254*, 83–91. https://doi.org/10.1016/j.pscychresns.2016.06.011

Bruggemann, J. M., Stockill, H. V, Lenroot, R. K., & Laurens, K. R. (2013). Mismatch

negativity (MMN) and sensory auditory processing in children aged 9 – 12 years

presenting with putative antecedents of schizophrenia ☆. *International Journal of*

Psychophysiology, *89*(3), 374–380. https://doi.org/10.1016/j.ijpsycho.2013.05.008

Centers for Disease Control and Prevention. (2016). Retrieved from http://www.cdc.gov

Cheng, S. C., & Schepp, K. G. (2016). Early Intervention in Schizophrenia: A Literature

Review. *Archives of Psychiatric Nursing*, *30*(6), 774–781.

https://doi.org/10.1016/j.apnu.2016.02.009

Daneault, J. G., Stip, E., Villeneuve, M., Rodriguez, J. P., Dubé, F., Blais, D., Beaudouin,

O. (2013). Genealogy of instruments for prodrome evaluation of psychosis.

Frontiers in Psychiatry, *4*(APR), 1–9. https://doi.org/10.3389/fpsyt.2013.00025

Dazzan, P., Morgan, K. D., Orr, K., Hutchinson, G., Chitnis, X., Suckling, J., Murray, R.

M. (2005). Different Effects of Typical and Atypical Antipsychotics on Grey Matter

in First Episode Psychosis: the AESOP Study. *Neuropsychopharmacology*, *30*(4), 765–774. https://doi.org/10.1038/sj.npp.1300603

Devrim-Üçok, M., Keskin-Ergen, Y., & Üçok, A. (2016). Lack of progressive reduction in P3 amplitude after the first episode of schizophrenia: A 6-year follow-up study. *Psychiatry Research*, *243*, 303–311. https://doi.org/10.1016/j.psychres.2016.02.065

Doeller, C. F., Opitz, B., Mecklinger, A., Krick, C., Reith, W., & Schröger, E. (2003). Prefrontal cortex involvement in preattentive auditory deviance detection: Neuroimaging and electrophysiological evidence. *NeuroImage*, *20*(2), 1270–1282. https://doi.org/10.1016/S1053-8119(03)00389-6

Dominguez, M. D. G., Wichers, M., Lieb, R., Wittchen, H. U., & Van Os, J. (2011). Evidence that onset of clinical psychosis is an outcome of progressively more persistent subclinical psychotic experiences: An 8-year cohort study. *Schizophrenia Bulletin*, *37*(1), 84–93. https://doi.org/10.1093/schbul/sbp022

Duncan, C. C., Barry, R. J., Connolly, J. F., Fischer, C., Michie, P. T., Näätänen, R., Van Petten, C. (2009). Event-related potentials in clinical research: Guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. *Clinical Neurophysiology*, *120*(11), 1883–1908. https://doi.org/10.1016/j.clinph.2009.07.045

First, M. B., & Tasman, A. (2011). *Clinical guide to the diagnosis and treatment of mental disorders*. John Wiley & Sons.

Ford, J. M. (1999). Schizophrenia: the broken P300 and beyond. *Psychophysiology*, *36*(6), 667–682. https://doi.org/10.1017/s0048577299990479

Ford, J. M., Mathalon, D. H., Kalba, S., Whitfield, S., Faustman, W. O., & Roth, W. T. (2001). Cortical responsiveness during talking and listening in schizophrenia: An

event-related brain potential study. *Biological Psychiatry*, *50*(7), 540–549.

https://doi.org/10.1016/S0006-3223(01)01166-0

Ford, J. M., Mathalon, D. H., Roach, B. J., Keedy, S. K., Reilly, J. L., Gershon, E. S., &

Sweeney, J. A. (2013). Neurophysiological evidence of corollary discharge function

during vocalization in psychotic patients and their nonpsychotic first-degree

relatives. *Schizophrenia Bulletin*, *39*(6), 1272–1280.

https://doi.org/10.1093/schbul/sbs129

Ford, J. M., Mathalon, D. H., Sullivan, E. V, Lim, K. O., & Pfefferbaum, A. (1994).

Effect of cortical gray matter, attention and schizophrenia on P300 amplitude.

Biological Psychiatry, *35*(9), 705. https://doi.org/http://dx.doi.org/10.1016/0006-

3223(94)90981-4

Ford, J. M., Roach, B. J., & Mathalon, D. H. (2010). Assessing corollary discharge in

humans using noninvasive neurophysiological methods.

https://doi.org/10.1038/nprot.2010.67

Gaebler, A. J., Mathiak, K., Koten, J. W., König, A. A., Koush, Y., Weyer, D., …

Zvyagintsev, M. (2015). Auditory mismatch impairments are characterized by core

neural dysfunctions in schizophrenia. *Brain*, *138*(5), 1410–1423.

https://doi.org/10.1093/brain/awv049

Garrido, M. I., Kilner, J. M., Stephan, K. E., & Friston, K. J. (2009). The mismatch

negativity: A review of underlying mechanisms. *Clinical Neurophysiology*, *120*(3),

453–463. https://doi.org/10.1016/j.clinph.2008.11.029

Germine, L., Benson, T. L., Cohen, F., & Hooker, C. I. L. (2013). Psychosis-proneness
and the rubber hand illusion of body ownership. *Psychiatry Research*, *207*(1–2), 45–
52. https://doi.org/10.1016/j.psychres.2012.11.022

Grace, A. A. (2016). Developmental dysregulation of the dopamine system and the
pathophysiology of schizophrenia. *Neurodevelopment and Schizophrenia.*, *17*(8),
273–294. https://doi.org/10.1038/nrn.2016.57

Grzella, I., Müller, B. W., Oades, R. D., Bender, S., Schall, U., Zerbin, D., … Sartory, G.
(2001). Novelty-elicited mismatch negativity in patients with schizophrenia on
admission and discharge. *Journal of Psychiatry and Neuroscience*, *26*(3), 235–246.

Harrison, P. J. (1999). The neuropathology of schizophrenia. A critical review of the data
and their interpretation. *Brain*, *122 (Pt 4*, 593–624.
https://doi.org/10.1093/brain/122.4.593

Heinks-Maldonado, T. H., Mathalon, D. H., Houde, J. F., Gray, M., Faustman, W. O., &
Ford, J. M. (2007). Relationship of imprecise corollary discharge in schizophrenia to
auditory hallucinations. *Archives of General Psychiatry*, *64*(3), 286–96.
https://doi.org/10.1001/archpsyc.64.3.286

Horváth, J., Czigler, I., Jacobsen, T., Maess, B., Schröger, E., & Winkler, I. (2008).
MMN or no MMN: No magnitude of deviance effect on the MMN amplitude.
Psychophysiology, *45*(1), 60–69. https://doi.org/10.1111/j.1469-8986.2007.00599.x

Howes, O. D., Kambeitz, J., Kim, E., Stahl, D., Slifstein, M., Abi-Dargham, A., & Kapur,
S. (2012). The nature of dopamine dysfunction in schizophrenia and what this means
for treatment. *Archives of General Psychiatry*, *69*(8), 776–86.
https://doi.org/10.1001/archgenpsychiatry.2012.169

Hsieh, M. H., Shan, J., Huang, W., Cheng, W., & Chiu, M. (2012). Auditory event-

related potential of subjects with suspected pre-psychotic state and fi rst‐ episode

psychosis. *Schizophrenia Research*, *140*(1–3), 243–249.

https://doi.org/10.1016/j.schres.2012.06.021

Javitt, D. C., Doneshka P., Grochowski S., Ritter, W. (1995). Impaired mismatch

negativity generation reflects widespread dysfunction of working memory in

schizophrenia. *Archives of General Psychiatry*, *52*(7), 550–558. Retrieved from

http://dx.doi.org/10.1001/archpsyc.1995.03950190032005

Kargel, C., Sartory, G., Kariofillis, D., Wiltfang, J., & Mu, B. W. (2014). Mismatch

Negativity Latency and Cognitive Function in Schizophrenia, *9*(4), 1–10.

https://doi.org/10.1371/journal.pone.0084536

Kayser, J., Tenke, C. E., Kroppmann, C. J., Alschuler, D. M., Ben-david, S., Fekri, S., …

Corcoran, C. M. (2013). Olfaction in the psychosis prodrome : Electrophysiological

and behavioral measures of odor detection. *International Journal of

Psychophysiology*, *90*(2), 190–206. https://doi.org/10.1016/j.ijpsycho.2013.07.003

Keshavan, M. S., DeLisi, L. E., & Seidman, L. J. (2011). Early and broadly defined

psychosis risk mental states. *Schizophrenia Research*, *126*(1–3), 1–10.

https://doi.org/10.1016/j.schres.2010.10.006

Kieffaber, P. D., Okhravi, H. R., Hershaw, J. N., & Cunningham, E. C. (2016). Clinical

Neurophysiology Evaluation of a clinically practical , ERP-based neurometric

battery : Application to age-related changes in brain function. *CLINICAL

NEUROPHYSIOLOGY*, *127*(5), 2192–2199.

https://doi.org/10.1016/j.clinph.2016.01.023

Kline, E., & Schiffman, J. (2014). Psychosis risk screening: A systematic review. *Schizophrenia Research*, *158*(1–3), 11–18. https://doi.org/10.1016/j.schres.2014.06.036

Kline, E., Wilson, C., Ereshefsky, S., Denenny, D., Thompson, E., Pitts, S. C., … Schiffman, J. (2012). Psychosis risk screening in youth: A validation study of three self-report measures of attenuated psychosis symptoms. *Schizophrenia Research*, *141*(1), 72–77. https://doi.org/10.1016/j.schres.2012.07.022

Kotlicka-Antczak, M., Pawełczyk, A., Karbownik, M. S., Pawełczyk, T., Strzelecki, D., Żurner, N., & Urban-Kowalczyk, M. (2016). Deficits in the identification of pleasant odors predict the transition of an at-risk mental state to psychosis. *Schizophrenia Research*. https://doi.org/10.1016/j.schres.2016.10.019

Krumpal, I. (2013). Determinants of social desirability bias in sensitive surveys: A literature review. *Quality and Quantity*, *47*(4), 2025–2047. https://doi.org/10.1007/s11135-011-9640-9

Kumari, V., & Postma, P. (2005). Nicotine use in schizophrenia: The self medication hypotheses. *Neuroscience and Biobehavioral Reviews*, *29*(6), 1021–1034. https://doi.org/10.1016/j.neubiorev.2005.02.006

Linden, D. E. J. (2005). The P300 : Where in the Brain Is It Produced and What Does It Tell Us ?, *11*(6), 563–576. https://doi.org/10.1177/1073858405280524

Lindín, M., Correa, K., & Díaz, F. (2013). Mismatch negativity (MMN) amplitude as a biomarker of sensory memory deficit in amnestic mild cognitive impairment, *5*(November), 1–10. https://doi.org/10.3389/fnagi.2013.00079

Luck, S. J., Mathalon, D. H., O'Donnell, B. F., Hmlinen, M. S., Spencer, K. M., Javitt, D. C., & Uhlhaas, P. J. (2011). A roadmap for the development and validation of event-related potential biomarkers in schizophrenia research. *Biological Psychiatry*, *70*(1), 28–34. https://doi.org/10.1016/j.biopsych.2010.09.021

Mathalon, D. H., Ford, J. M., & Pfefferbaum, A. (2000). Trait and State Aspects of P300 Amplitude Reduction in Schizophrenia : A Retrospective Longitudinal Study, *3223*(99).

McCarley, R. W., Salisbury, D. F., Hirayasu, Y., Yurgelun-Todd, D. a, Tohen, M., Zarate, C., … Shenton, M. E. (2002). Association between smaller left posterior superior temporal gyrus volume on magnetic resonance imaging and smaller left temporal P300 amplitude in first-episode schizophrenia. *Archives of General Psychiatry*, *59*(4), 321–331. https://doi.org/10.1001/archpsyc.59.4.321

Michie, P. T., Innes-brown, H., Todd, J., & Jablensky, A. V. (2002). Duration Mismatch Negativity in Biological Relatives of Patients with Schizophrenia Spectrum Disorders.

Murphy, J. R., Rawdon, C., Kelleher, I., Twomey, D., Markey, P. S., Cannon, M., & Roche, R. A. P. (2013). Reduced duration mismatch negativity in adolescents with psychotic symptoms : further evidence for mismatch negativity as a possible biomarker for vulnerability to psychosis. *BMC Psychiatry*, *13*(1), 1. https://doi.org/10.1186/1471-244X-13-45

Naätaïnen, R. (2008). Mismatch negativity (MMN) as an index of central auditory system plasticity, *47*, 16–20. https://doi.org/10.1080/14992020802340116

Naˉaˉtaˉnen, R., Pakarinen, S., Rinne, T., & Takegata, R. (2004). The mismatch negativity

(MMN): towards the optimal paradigm, *115*, 140–144.

https://doi.org/10.1016/j.clinph.2003.04.001

Näätänen, R., Lehtokoski, a, Lennes, M., Cheour, M., Huotilainen, M., Iivonen, a, …

Alho, K. (1997). Language-specific phoneme representations revealed by electric

and magnetic brain responses. *Nature*.

Nagai, T., Tada, M., Kirihara, K., Araki, T., Jinde, S., & Kasai, K. (2013). Mismatch

negativity as a " translatable " brain marker toward early intervention for psychosis :

a review, *4*(September), 1–10. https://doi.org/10.3389/fpsyt.2013.00115

Nagai, T., Tada, M., Kirihara, K., Yahata, N., Hashimoto, R., Araki, T., & Kasai, K.

(2013). Auditory mismatch negativity and P3a in response to duration and frequency

changes in the early stages of psychosis. *Schizophrenia Research*, *150*(2–3), 547–

554. https://doi.org/10.1016/j.schres.2013.08.005

Neuhaus, A. H., Brandt, E. S. L., Goldberg, T. E., Bates, J. A., & Malhotra, A. K. (2013).

Evidence for impaired visual prediction error in schizophrenia. *Schizophrenia

Research*, *147*(2–3), 326–330. https://doi.org/10.1016/j.schres.2013.04.004

Neuhaus, A. H., Popescu, F. C., Rentzsch, J., & Gallinat, J. (2013). Critical Evaluation of

Auditory Event-Related Potential De cits in Schizophrenia : Evidence From Large-

Scale Single-Subject Pattern Classi cation, 1–10.

https://doi.org/10.1093/schbul/sbt151

Niendam, T. A., Jalbrzikowski, M., & Bearden, C. E. (2009). Exploring predictors of

outcome in the psychosis prodrome: Implications for early identification and

intervention. *Neuropsychology Review*, *19*(3), 280–293.

https://doi.org/10.1007/s11065-009-9108-z

Nowak, K., Oron, A., Szymaszek, A., Leminen, M., & Näätänen, R. (2016).

Electrophysiological Indicators of the Age-Related Deterioration in the Sensitivity

to Auditory Duration Deviance, *8*(January), 1–10.

https://doi.org/10.3389/fnagi.2016.00002

Oestreich, L. K. L., Mifsud, N. G., Ford, J. M., Roach, B. J., Mathalon, D. H., &

Whitford, T. J. (2015). Cortical Suppression to Delayed Self-Initiated Auditory

Stimuli in Schizotypy : Neurophysiological Evidence for a Continuum of Psychosis.

https://doi.org/10.1177/1550059415581708

Oestreich, L. K. L., Mifsud, N. G., Ford, J. M., Roach, B. J., Mathalon, D. H., &

Whitford, T. J. (2015). Subnormal sensory attenuation to self-generated speech in

schizotypy : Electrophysiological evidence for a " continuum of psychosis ."

International Journal of Psychophysiology, *97*(2), 131–138.

https://doi.org/10.1016/j.ijpsycho.2015.05.014

Olsen, K. A., & Rosenbaum, B. (2006). Review article Prospective investigations of the

prodromal state of schizophrenia : assessment instruments, 273–282.

https://doi.org/10.1111/j.1600-0447.2005.00698.x

Opitz, B., Rinne, T., Mecklinger, A., Cramon, D. Y. Von, & Schro, E. (2002).

Differential Contribution of Frontal and Temporal Cortices to Auditory Change

Detection : fMRI and ERP Results, *174*, 167–174.

https://doi.org/10.1006/nimg.2001.0970

Os, J. I. M. V. A. N. (2003). Invited Paper Is there a continuum of psychotic experiences

in the general population ?, 242–252.

Os, J. Van, Linscott, R. J., Delespaul, P., & Krabbendam, L. (2009). I N V IT E D R E V

IE W A systematic review and meta-analysis of the psychosis continuum : evidence

for a psychosis proneness – persistence – impairment model of psychotic disorder,

179–195. https://doi.org/10.1017/S0033291708003814

Pakarinen, S., Takegata, R., Rinne, T., Huotilainen, M., & Na ̈a ̈ta ̈nen, R. (2007).

Measurement of extensive auditory discrimination profiles using the mismatch

negativity (MMN) of the auditory event-related potential (ERP), *118*, 177–185.

https://doi.org/10.1016/j.clinph.2006.09.001Peled, A., Ritsner, M., Hirschmann, S.,

Geva, A. B., & Modai, I. (2000). Touch Feel Illusion in Schizophrenic Patients.

Polich, J. (2009). NIH Public Access, *118*(10), 2128–2148.

https://doi.org/10.1016/j.clinph.2007.04.019.Updating

Qiu, Y., Tang, Y., Chan, R. C. K., Sun, X., & He, J. (2014). P300 Aberration in First-

Episode Schizophrenia Patients: A Meta-Analysis. *PLoS ONE*, *9*(6), e97794.

https://doi.org/10.1371/journal.pone.0097794

Rajji, T. K., Ismail, Z., & Mulsant, B. H. (2009). Age at onset and cognition in

schizophrenia :, 286–293. https://doi.org/10.1192/bjp.bp.108.060723

Rössler, W., Riecher-Rössler, A., Angst, J., Murray, R., Gamma, A., Eich, D., … Gross,

V. A. (2007). Psychotic experiences in the general population: A twenty-year

prospective community study. *Schizophrenia Research*, *92*(1–3), 1–14.

https://doi.org/10.1016/j.schres.2007.01.002

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., …
Greicius, M. D. (2007). Dissociable Intrinsic Connectivity Networks for Salience
Processing and Executive Control, *27*(9), 2349–2356.
https://doi.org/10.1523/JNEUROSCI.5587-06.2007

Shen, C., Popescu, F. C., Hahn, E., Ta, T. T. M., Dettling, M., & Neuhaus, A. H. (2014).
Neurocognitive pattern analysis reveals classificatory hierarchy of attention deficits
in Schizophrenia. *Schizophrenia Bulletin*, *40*(4), 878–885.
https://doi.org/10.1093/schbul/sbt107

Simons, C. J. P., Sambeth, A., Krabbendam, L., Pfeifer, S., Os, J. Van, & Riedel, W. J.
(2011). Clinical Neurophysiology Auditory P300 and N100 components as
intermediate phenotypes for psychotic disorder : Familial liability and reliability.
Clinical Neurophysiology, *122*(10), 1984–1990.
https://doi.org/10.1016/j.clinph.2011.02.033

Simons, M., & Nave, K. (2016). Oligodendrocytes : Myelination and Axonal. *Cold
Spring Harbor perspectives in biology* https://doi.org/10.1101/cshperspect.a020479

Stekelenburg, J. J., Pieter, J., Gool, A. R. Van, Sitskoorn, M., & Vroomen, J. (2013). De
fi cient multisensory integration in schizophrenia : An event-related potential study.
Schizophrenia Research, *147*(2–3), 253–261.
https://doi.org/10.1016/j.schres.2013.04.038

Stelt, O. Van Der, & Belger, A. (2007). Application of Electroencephalography to the
Study of Cognitive and Brain Functions in Schizophrenia, *33*(4), 955–970.
https://doi.org/10.1093/schbul/sbm016

Tamnes, C. K., Østby, Y., Fjell, A. M., Westlye, T., Due-tønnessen, P., & Walhovd, K. B. (2010). Brain Maturation in Adolescence and Young Adulthood : Regional Age-Related Changes in Cortical Thickness and White Matter Volume and Microstructure, *i*(March). https://doi.org/10.1093/cercor/bhp118

Todd, J., Harms, L., Schall, U., & Michie, P. T. (2013). Mismatch negativity : translating the potential, *4*(December), 1–22. https://doi.org/10.3389/fpsyt.2013.00171

Todd, J., Michie, P. T., Schall, U., Ward, P. B., & Catts, S. V. (2012). Mismatch negativity (MMN) reduction in schizophrenia — Impaired prediction-error generation , estimation or salience ? *International Journal of Psychophysiology*, *83*(2), 222–231. https://doi.org/10.1016/j.ijpsycho.2011.10.003

Towle, V. L., Bolaños, J., Suarez, D., Tan, K., Grzeszczuk, R., Levin, D. N., … Spire, J. P. (1993). The spatial location of EEG electrodes: locating the best-fitting sphere relative to cortical anatomy. *Electroencephalography and Clinical Neurophysiology*, *86*(1), 1–6. https://doi.org/10.1016/0013-4694(93)90061-Y

Umbricht, D., & Krljes, S. (2005). Mismatch negativity in schizophrenia : a meta-analysis, *76*, 1–23. https://doi.org/10.1016/j.schres.2004.12.002

Vita, A., De Peri, L., Deste, G., & Sacchetti, E. (2012). Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies. *Translational Psychiatry*, *2*(11), e190. https://doi.org/10.1038/tp.2012.116

Whitford, T. J., Ford, J. M., Mathalon, D. H., Kubicki, M., & Shenton, M. E. (2012). Schizophrenia , Myelination , and Delayed Corollary Discharges : A Hypothesis, *38*(3), 486–494. https://doi.org/10.1093/schbul/sbq105

Wood, S. J., Pantelis, C., Velakoulis, D., Fornito, A., & Mcgorry, P. D. (2008).

Progressive Changes in the Development Toward Schizophrenia : Studies in

Subjects at Increased Symptomatic Risk, *34*(2), 322–329.

https://doi.org/10.1093/schbul/sbm149

Yoon, Y. B., Yun, J., Jung, W. H., & Cho, K. I. K. (2015). Altered Fronto-Temporal

Functional Connectivity in Individuals at Ultra-High-Risk of Developing Psychosis.

https://doi.org/10.1371/journal.pone.0135347

Yung, A. R., & McGorry, P. D. (1996). The prodromal phase of first-episode psychosis:

past and current conceptualizations. *Schizophr Bull*, *22*(2), 353–370.

https://doi.org/10.1093/schbul/22.2.353

Appendix A

Abbreviated Youth Psychosis At Risk Questionnaire (YPARQ-B)

Mark 'Y' for yes if the question completely or mostly applies to you, mark 'N' for no if the question completely or mostly does not apply to you and mark 'U' if you are undecided. If you do not understand a question or do not want to answer it, leave it blank.

1. Are you more superstitious than other people?	Y N U
2. Do you hold beliefs that others would find unusual or different or bizarre?	Y N U
3. Do you ever feel you can predict the future?	Y N U
4. Have you felt that something outside yourself has been controlling your thoughts, feelings or actions?	Y N U
5. Do you ever feel that the world does not exist?	Y N U

6. Do familiar surroundings sometimes seem threatening to you?	Y N U
7. Have you ever felt that some person or force interferes with your train of thinking?	Y N U
8. Are your thoughts broadcast so that other people know what you are thinking?	Y N U
9. Do you ever feel people are plotting against you or planning to harm you?	Y N U
10. Do you feel you have unusual healing abilities or powers?	Y N U
11. Do things sound softer than usual to you?	Y N U
12. Do you ever hear the voice of someone talking that other people cannot hear?	Y N U
13. Do things that you see appear different in color, brighter or duller or in some other way changed?	Y N U
14. Is it hard to establish a connection or do you feel at a distance when talking to others?	Y N U
15. Have you noticed any unusual bodily sensations such as tingling, pulling, pressure, burning, cold, vibrations, drilling, tearing or electricity?	Y N U

16. Do people ever say you do odd or strange things?	Y N U
17. Have you felt at a distance from yourself, as if you were outside your own body?	Y N U
18. Do you tend to avoid social activities with others?	Y N U
19. Do you ever hear sounds that are not there?	Y N U
20. Do familiar surroundings sometimes seem unreal to you?	Y N U
21. Do you ever feel that things or parts in your body are working differently?	Y N U
23. Have you ever felt that you don't exist or are dead?	Y N U
24. Do you get strange feelings on or just beneath your skin?	Y N U
25. Have you had the sense that some person or force is around you, even though you cannot see anyone?	Y N U
26. Do things sound louder than usual to you?	Y N U
27. Do people ever say your ideas are strange or don't make sense?	Y N U

28. Have you ever felt that some one was playing with your mind?	Y N U

Appendix B

Prime Screen

Based on your experiences within the past year, please indicate how much you agree or disagree with the following statements.

Within the past year:	Definitely disagree	Somewhat disagree	Slightly disagree	Not sure	Slightly agree	Somewhat agree	Definitely agree
1. I think that I have felt that there are odd or unusual things going on that I can't explain.	0	1	2	3	4	5	6
2. I think that I might be able to predict the future.	0	1	2	3	4	5	6
3. I may have felt that there could possibly be something interrupting or controlling my thoughts, feelings, or actions.	0	1	2	3	4	5	6
4. I have had the experience of doing something differently	0	1	2	3	4	5	6

because of my superstitions.							
5. I think that I may get confused at times whether something I experience or perceive may be real or may be just part of my imagination or dreams.	0	1	2	3	4	5	6
6. I have thought that it might be possible that other people can read my mind, or that I can read other's minds.	0	1	2	3	4	5	6
7. I wonder if people may be planning to hurt me or even may be about to hurt me.	0	1	2	3	4	5	6
8. I believe that I have special natural or supernatural gifts beyond my talents and natural strengths.	0	1	2	3	4	5	6
9. I think I might feel like my mind is 'playing tricks' on me.	0	1	2	3	4	5	6
10. I have had the experience of hearing faint or clear sounds of people or a person mumbling or talking when there is no one near	0	1	2	3	4	5	6

me.							
11. I think that I might hear my own thoughts being said out loud.	0	1	2	3	4	5	6
12. I have been concerned that I might be 'going crazy.'	0	1	2	3	4	5	6

ERP DIFFERENCES ACROSS A PSYCHOSIS CONTINUUM

Appendix C

<u>Language Questionnaire</u>

Gender: Male   Female   Other

Age: _____Years of Education: _____

1. What is your mother tongue (the first language you learned)?

2. What other languages do you know?

3. What is your best language for speaking?

4. What is your best language for writing?

5. What language(s) did your family speak at home?

6. In what city (and country) were you born?

7. How long did you live in the city that you were born?

8. In what city did you go to elementary school?

9. In what city did you go to high school?

10. How many years have you lived in Canada?

11. Do you have any formal musical training (vocal or instrumental)? If so, please indicate how old you were when you received this training and how many years you studied.

ERP DIFFERENCES ACROSS A PSYCHOSIS CONTINUUM

Appendix D

<u>Handedness Questionnaire</u>

Instructions: Think carefully about each of the following tasks and indicate by circling, whether you use your left hand, right hand or either hand.

1. Which hand do you use to hold scissors?

  Left Either Right

2. With which hand do you draw?

  Left Either Right

3. With which hand do you screw the top off a bottle?

  Left Either Right

4. With which hand do you deal cards?

  Left Either Right

5. Which hand do you use to hold a toothbrush when cleaning teeth?

  Left Either Right

6. With which hand do you use a bottle opener?

  Left Either Right

7. With which hand do you throw a ball away?

  Left Either Right

8. Which hand do you use to hold a hammer?

  Left Either Right

9. With which hand do you thread a needle?

  Left Either Right

10. With which hand do you hold a racket when playing tennis?

Left   Either   Right

11. With which hand do you open the lid of a small box?

Left   Either   Right

12. With which hand do you turn a key?

Left   Either   Right

13. With which hand do you cut a cord with a knife?

Left   Either   Right

14. With which hand do you stir with a spoon?

Left   Either   Right

15. With which hand do you use an eraser on paper?

Left   Either   Right

16. With which hand do you strike a match?

Left   Either   Right

17. With which hand do you write?

Left   Either   Right